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SHFOOD AND DRUG ADMINISTRATION

FDA GUIDANCE ON CLINICAL TRIAL

DATA MONITORING COMMITTEES (DMCs)

OPEN PUBLIC MEETING

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C O N T E N T S

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P R O C E E D I N G S

WELCOME

DR. LEPAY: Good morning. On behalf of FDA I'd like to welcome you to today's workshop on data monitoring committees. The purpose of this workshop is to introduce FDA's new guidance for clinical trial sponsors on the establishment and operation of clinical trial data monitoring committees.

We planned this workshop several months ago with the expectation certainly that this guidance document would be out with ample time for individuals to review it in advance of the workshop. We may not have had quite as much time for this review process as we would have hoped but we are very pleased to at least see that the document is available and is, in fact, available for general circulation today outside.

I want to start by just mentioning, of course, that this guidance document has been a while in planning, in preparation and in clearance. We've certainly been talking about it at FDA for well over a year now and it is a very integral part of our move certainly to look at subject safety, subject protection in real-time and as part of our overall unit of overseeing clinical trials respective to FDA's regulatory responsibilities.

The draft guidance came out just about a week ago, announced in the Federal Register on the 20th of November, and for those who otherwise need to access it by means other than the formal copies that have been distributed at the outside of this conference room, it is available on various of FDA's websites, either through the CBER website, www.fda.gov/cber/guidelines/clindatmon.htm. Or if you can't remember that, simply go to FDA's general website, www.fda.gov, to the clinical trials section and you'll see this in the What's New? and in the New Guidances Section.

We're currently in the beginning of a 90-day comment period, which began at the time of publication of this guidance in the Federal Register. The comment period will be open until the 19th of February 2002. Comments can and should be submitted to a docket which has been established for this purpose. The identification of this docket is listed here, 01D-0489. In fact, we can accept comments either in writing directly to the Dockets Management Branch at the address shown here, and this is also provided in the Federal Register announcement, or more simply as electronic comments again off of the FDA website at a specific link to our Dockets Management Section. Again you'll need to reference the docket number.

We think this meeting is a very important step in providing us with input on this guidance document. As we've remarked many times over the past several years, public comment is integral to the process of FDA rulemaking and development of guidances. Certainly what we're going to be talking about today in the presentations that you will hear reflect FDA's current thinking in the area of data monitoring committees but clearly that thinking is very much an interactive process that depends on the contributions of everyone here in the audience, as well as those at your respective companies or institutions who we strongly encourage to read and provide comments to us.

So with that, I'm going to open the meeting.

Oh, let me also remind everyone here that the proceedings of this meeting are being audio-recorded. The transcripts of this meeting will be made available, as well as transcripts will be filed to the docket, so comments made here will, in fact, be captured and will be part of our consideration as we review the guidance document and move forward toward its finalization.

And with that, I would then like to introduce our opening speaker and I have the very great pleasure of presenting Dr. Greg Koski, who's head of the Office for Human Research Protection in the Department of Health and Human Services. Greg has certainly been a tremendous

moving force in the area of human subject protection since he came on board just a little over a year ago and has been an extremely important and successful colleague with FDA in moving forward initiatives pertaining to human subject protection and the oversight of clinical trials.

So with that, I'll ask Greg to open the meeting with a few introductory remarks.

OPENING REMARKS

DR. KOSKI: Thank you very much, David, for the kind words. It's really a pleasure to be here. It's nice to see so many people out there, as well. You know, we've been accused in government of holding public meetings in order to get more people to come to Washington in order to support the economy. I hope that some of you have come from farther than Bethesda or downtown, but it's great to see all of you here. I think it reflects the very high level of interest in this very important topic as it pertains not only to the oversight of research, protecting the validity and the objectivity of the research, but also protection of human subjects.

I'm sure that all of you recognize that over the last 30 years or so the FDA and the former Office for Protection from Research Risks have shared responsibility for protection of human subjects in research. Since the Office for Human Research Protections was created a little

over a year ago, not only have we continued that tradition of collaboration but indeed have worked very, very hard to strengthen it as we go forward and I think that David has been absolutely critical to the success of that effort.

I think all of you are aware that the system for protection of human subjects in research is undergoing some remodeling currently. Over these last 30 years we've really had two schemes under which we have operated, that which applied primarily to federally supported and conducted research, a system that really focussed primarily on an assurance process before research was to be initiated, whereas we had a system that FDA was primarily responsible for that dealt largely with corporate sponsored, privately sponsored research that focussed far less on an up-front assurance process but instead focussed very significantly on audits of investigators and IRBs and sponsors in order to ensure the process.

And while both of these approaches, they have good reasons for their existence, have had both strengths and weaknesses, when the Office of the Inspector General and the General Accounting Office looked at our processes they both concluded that although each of these emphasized particular areas, there was a gap and that gap that they identified as a weakness in the overall process was in that area that I describe as what happens after the IRB says

okay. In other words, it's when we're actually conducting the research activities.

Clearly we do have processes for reporting adverse events, for interacting with investigators and subjects. We have seen data and safety monitoring boards utilized effectively over the years. But as we've gone forward we've begun to realize that indeed there are opportunities to utilize the stronger aspects of each of these systems in a more effective way and this effort by FDA, in conjunction with the rest of the colleagues here in the Department of Health and Human Services, to provide guidance on data monitoring committees I think is a very, very important step toward achieving a greater level of uniformity and to provide a component of the system that can work across the entire domain, which, of course, is something that we're very anxious to achieve.

So this document that has just been published a week ago with some relief, I believe, to everyone, it reflects the enormous effort and thinking that has gone into this by the folks at FDA, with input from many others, toward defining these committees, how they should be constituted, how they might be positioned, how they can interact with the IRBs and with investigators and sponsors as they carry out their important activities.

And in bringing this document forward I think it's quite clear that FDA is emphasizing the fact that this is not a fait accompli. This is a piece of work that they have put out there in order to stimulate discussion, to get your input, and today I think they're very, very serious in asking you to interact with them, with the panels. I think it's very interesting and also rewarding, I find, satisfying that if you look at the agenda for today's meeting, if you look at the participants in the panels, as well as here in the audience, you can see that there is a coming together of the minds of these two systems in important ways so that what we hope will emerge from this again will be a set of guidance that will strengthen the process for everyone.

There's an awful lot to talk about here today. Again we encourage you to really jump in, get involved in the discussions so that the final product is one that will serve everyone's interest.

With that, David, I wish you the very best of luck, and Susan, in your meeting today. I encourage you to take it seriously and get down to business. Thank you very much.

DR. LEPAY: Very good. With that, we'll begin with the discussion of our guidance document. Our first presentation this morning will be by Susan Ellenberg, who

chaired the working group involved with the drafting of this guidance document. Susan will outline the history and background of data monitoring committees. With that, I will turn this over to Susan and with luck, hopefully she can get us started on track here.

HISTORY AND BACKGROUND OF DMCs

DR. ELLENBERG: I'm very glad to see all of you here today. I notice there's still a few empty seats, mostly toward the front. So people who are coming in in the back, don't be shy; just wander up and you'll find a seat.

Let's start with a definition of a data monitoring committee. This is the definition exactly as it appears in our document. It may not be everybody's favorite definition but I think it's serviceable. A data monitoring committee is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an on-going clinical trial. The data monitoring committee advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

So this is the kind of committee that we're going to be talking about today. Many of you have seen this slide. I just would like to clarify on the terminology.

We are talking about data monitoring committees but these committees have gone by a lot of other kinds of names, so you can pick as many as you like from column A and put it together with something from column B and something from column C and I don't know whether all the permutations and combinations have been used but many of them have been. In particular, the other phrase that's used frequently is data safety monitoring board. As far as I've been able to ascertain, all of these things mean approximately the same thing and are consistent with the definition.

We are using the phrase data monitoring committees because that is the terminology that was selected by the International Conference on Harmonization, who, as I'll talk about in a minute, is a collaboration of industry and regulatory scientists in the United States, Europe and Japan who are putting together guidance documents on regulated clinical trials and other aspects of regulated research and have used this phrase, so we're being consistent with that.

In the document we mention some other oversight groups because it's important to recognize that the data monitoring committee, while there may be some overlap of oversight, is a separate group from any of these others. Many trials have a steering committee. This is an internal group to the trial. This is the trial leadership who

designs the trial, monitors the conduct of the trial, will prepare the final presentation. That is an internal group where a data monitoring committee is an external group.

Institutional review boards, sometimes called institutional ethics committees, are charged with evaluating the acceptability and appropriateness of a trial in a specific clinical setting. While they have some oversight responsibility as the trial progresses, it's not at the level of detail and looking at specific data that the data monitoring committee has. So again there is a difference. These are not the same groups.

Another kind of oversight committee that would be internal to a trial would be an end point assessment or an end point adjudication committee. This is a committee often of trial participants who would review data on the reported primary outcomes to ensure consistency with the protocol specified criteria--for example, to look at reports of an acute myocardial infarction and make sure that all the data were there to meet the protocol criteria.

There are often in trials also site monitoring groups. The responsibility of these groups is to basically do an overall quality control. They may go out to the sites, look at the data, make sure that what's in the record is consistent with what's on the form. Again that's another type of oversight but it's different from the kind

of monitoring that we're talking about here that a data monitoring committee would do.

When did data monitoring committees start? This is one story that I've heard other people may have other stories, but in a clinical trial that the NIH sponsored back in the 1960s called the University Group Diabetes Project several investigational anti-diabetic agents were compared to placebo and this, you have to remember, was sort of the very beginning of clinical trials. Randomized clinical trials were brand new in the 1960s. There were no oversight groups. There was a group of investigators who were mounting this trial and I notice that increased cardiovascular mortality was emerging early for one of the agents, not what was expected in this trial. These agents were hoped to improve mortality. There was no established statistical monitoring plan. This was well before the era of statistically based sequential designs and the investigators and sponsors were wringing their hands, not really sure what to do about this, but their gut feeling was let's get some outside experts who are not invested in the trial in the way we are to have a fresh look, to help us really make the best decision we possibly can, based on the data.

So it was this sense of needing some objective kind of look that may have led to a recognition that it

would be generally good to have some kind of external advice on this sort of thing.

In 1967 a report was issued to what was then the National Heart Institute, now NHLBI, regarding the conduct of clinical trials. This report is widely referred to as the Greenberg Report because the committee that put it together was chaired by Dr. Bernard Greenberg, who was chair of the Department of Biostatistics at the University of North Carolina. This covered the range of good clinical trials practices for that time and it included a recommendation that a formal committee be established to review the accumulating data on safety, efficacy and trial conduct.

I don't think the phrase data safety monitoring board or data monitoring committee was used in this report. It was published after a number of years ultimately in Controlled Clinical Trials in 1988 so if you're interested in the report, you can find it there.

I'm not going to say too much about history. Data monitoring committees have been components of federally funded trials for a very long time, particularly the NIH and the VA, but there are probably other agencies, as well. Department of Defense and CDC have done clinical trials probably that have used data monitoring committees. They've been used primarily in multi-centered trials with

mortality end points or end points of major morbidity, things that will have a permanent impact on people's fundamental health.

And the reason that these committees have been felt to be needed for these kinds of trials is because in these trials efficacy and safety end points essentially overlap. If you have a mortality end point and you expect to see deaths in the course of the study, if you have a safety problem with your drug where there's excess mortality, you can't really see that by looking at individual cases. You need to look overall at the number of deaths being observed. So it's an efficiency end point but it's also a safety end point and somebody needs to be looking as the trial progresses to see if there's any kind of difference emerging.

Because of the importance of these end points, there's a real ethical imperative to monitor. If the trial is part-way through and it's very clearly established that more lives are being preserved on one arm than the other, it would be important not to continue to enter patients on that trial. And as was noted in the UGDP example, there is a need, because the stakes are so high, a need to insert some objectivity into the interim assessments, to try and make sure that the decisions that are made are based on the

data and not on possible extraneous influences from which few of us are free.

Now in industry data monitoring committees were not used so frequently in industry trials prior to the 1990s. For some trials they were used, particularly trials with mortality end points, primarily but not entirely in the cardiovascular area. But recently there's been a lot more use of data monitoring committees in industry trials for some of these reasons. Industry is sponsoring more trials with mortality end points or other major end points. Again we're still in an early phase of evolution of clinical trials methodology. There's been a heightened awareness of the value of independent monitoring in some of these circumstances, I think, and there's also, I think, increased government-industry collaboration that has introduced industry to some of the data monitoring approaches that have long been used in trials that are sponsored by government agencies.

Now data monitoring committees are almost entirely absent in FDA regulations. There's only one type of trial that actually requires a data monitoring committee and those are trials in which informed consent is waived. And some of you will remember that a regulation was issued in 1996 dealing with emergency research in which informed consent was simply not feasible, and I have the CFR

reference up there. Why would it not be feasible? If a patient is unconscious or otherwise unable to provide consent and no proxy can be available within the time frame in which treatment would be required to be started.

So this was a regulation aimed specifically at being able to do research in this kind of circumstance but the circumstances were very limited. There was great concern at FDA and outside the FDA about allowing a trial to proceed without informed consent. It had to be a life-threatening situation. The trial could not be feasible without the waiver. There had to be a strong scientific basis established for the investigational treatment.

And because we were not having such a fundamental protection as informed consent, additional protections were required in such trials, such as prior community consultation, public notification, and the establishment of an independent data monitoring committee. So this is the only place where data monitoring committees had been required.

Data monitoring committees have been mentioned in several FDA guidance documents, mostly those developed through the International Conference on Harmonization, including the E3 document, Structure and Content of Clinical Study Reports, E6, the Good Clinical Practice

document, and E9, Statistical Principles for Clinical Trials.

E3, this is sort of an after-the-fact document. It tells you how to report once you've completed the trial and it says well, if you had a data monitoring committee you've got to tell us about it. Who was on it? How did it operate? What statistical monitoring plan was used? How did you make sure that people who were supposed to be blinded stay blinded? You need to describe the interim analysis and you need to provide all the minutes of the meetings and the interim data reports. So that's in one of the guidance documents.

E6, the Good Clinical Practice document, has a section that mentions the independent data monitoring committee, basically provides a sort of definition and specifies that it should have written operating procedures and maintain written records. So it's not a whole lot of detail.

A little more detail in the E9 document, Statistical Principles for Clinical Trials. Again it notes what a data monitoring committee does. It evaluates interim data and makes recommendations to the sponsor--that it should have written operating procedures and maintain meeting records. This is the first document where the notion of confidentiality of interim data is mentioned and

the protection of the trial integrity, that an independent data monitoring committee will help with those. It notes that it is separate from an IRB or an IEC, not the same thing, that its composition is multidisciplinary, and it notes that if there are sponsor representatives participating in the data monitoring activities, then those roles must be clearly defined and it must be clearly understood how interim results within a sponsoring organization would be controlled.

So today data monitoring committees are increasingly used. NIH and the various NIH institutes have established policies requiring data monitoring committees for many extramural and intramural trials and you can find those guidelines on the NIH websites.

Data monitoring committees have become a standard in industry trials with major end points, for the most part, and they've been suggested even for some early phase trials when you have a novel high-risk treatment and we're going to be discussing some of those possibilities.

There are a variety of models for data monitoring committee operation. People who have been doing this for a long time--I've talked to a lot of people and different people do it different ways and most people think that their way is right, so I would not say that there is an absolute consensus on what the optimal approach is and

there may be multiple approaches that could be acceptable in any given circumstance.

In 1998 the Office of the Inspector General of HHS issued a report on institutional review boards and while the focus was on IRBs, there were two recommendations that dealt specifically with data monitoring committees.

The first recommendation was that data monitoring committees be required for trials under NIH and FDA purview that meet specified conditions, didn't say what those conditions would be but said that NIH and FDA would need to define those conditions and would need to specify requirements for data monitoring committee composition.

Well, this document is, in a sense, a response to this, although the word "required" doesn't really fit with a guidance document but we have tried to respond to this recommendation.

The second recommendation was that data monitoring committees should have primary responsibility for reviewing and evaluating adverse experiences occurring in the trial and that data monitoring committee assessments, along with summary data, could be shared with IRBs. We've certainly had a lot of discussion about this. We're not entirely sure that the data monitoring committee is the best place for primary responsibility for review of individual adverse events, although they certainly do have

a role overall in considering adverse events in a trial and I think we'll have some discussion of that.

The development of this guidance was a joint effort of three FDA centers plus the Office of the Commissioner. Center for Biologics, Center for Drugs, Center for Devices and Radiological Health all were involved in the development of this document, as well as the Office of Good Clinical Practice, the new Office of Good Clinical Practice headed by Dr. Lepay.

We did get interim comments, very helpful interim comments from our colleagues at NIH on this document. We also solicited some interim comments from two FDA advisors that were considered in putting together what is our final draft.

And you've seen this slide. This is the title of the guidance document.

Just a couple of introductory comments to the document before I turn this over to Dr. Campbell. The document frequently refers to the sponsor and there could be a question as to who is the sponsor, who acts as the sponsor. Generally at FDA we regard the sponsor as the group, the organization that holds the IND but we acknowledge in the opening of the document that sometimes sponsors delegate authority for decision-making to some entity. It could be a steering committee, could be a

contract research organization or even a principal investigator. And when you read the sponsor does this or the sponsor may do this in the document, you should also read the group, the entity to whom the sponsor may have delegated such decision-making authority. It seemed awkward to continue to write "or the steering committee" or whatever throughout the document. So that should be understood. The sponsor may be a company or may be a government agency.

We discuss briefly the issue of government and industry sponsors. We believe the issues discussed in this guidance document are relevant to all trials, whatever the sector of the sponsor, so we don't distinguish between government and industry sponsors but we do recognize that there are differences in type and extent of conflict of interest that exist for government and industry sponsors and those may have implications for the types of data monitoring committee approaches that are established.

Now the intent of this guidance document is to describe generally acceptable models for data monitoring committee establishment and operation, to discuss possible advantages and disadvantages of different approaches, and very importantly, to increase awareness of the potential concerns that can arise in trials when comparative data are subject to interim monitoring and we've had some experience

with this, which we'll be discussing today. I know that some of these issues I had not been aware of before coming to FDA so I think it is important to consider these.

We also address the relationship of data monitoring committees to the regulatory requirements for monitoring and reporting, to understand who maintains who responsibility.

What it's not intended to be is prescriptive. It's not intended to lay out the exact single model of data monitoring committees that everything should adhere to. We are really trying to raise issues and help those who are sponsoring clinical trials to understand what some of the issues are so that we can develop optimal strategies.

That's it. Thank you for your attention.

DR. LEPAY: Thank you, Susan. I think that was a very good introduction to our guidance document today, to some of the history on data monitoring committees.

We've organized the program today in three sections, as you'll see, with ample opportunity for both open discussion as well as panel discussion with each of these sections.

The first section covers the chapters 1 through 3 of the guidance document and with that, I will turn over to Greg Campbell for our second presentation. Greg is the director of the Division of Biostatistics in the Center for

Devices and Radiological Health and he will be talking about certainly one of the most important topics addressed within this guidance document, some of the thinking behind which trials need data monitoring committees.

WHICH TRIALS NEED DATA MONITORING COMMITTEES?

DR. CAMPBELL: Thank you, David.

Well, I get the pleasure of trying to explain when one should consider using a data monitoring committee and when not.

The first question and the important one, I suppose, is are data monitoring committees always needed or always advised? And the answer quite simply is no, that there are lots of situations where it's less than clear that a data monitoring committee would be helpful. Although it's not advised in every trial, there are advantages, there are situations where a data monitoring committee might prove valuable.

So Susan Ellenberg in her opening remarks mentioned that there is a situation where a data monitoring committee is required and it's in the case where one is dealing with some emergency therapy and there is waived informed consent. An example of this would be the automatic external defibrillators that you see now in airports and sometimes on airplanes. Those external defibrillators were tested in a clinical trial with a data

monitoring committee. What one needs there is to act very quickly. There's no possibility of informed consent except as a community, and that's an example where the DMC is required.

What is clear and what is in the regulations is that all clinical trials do require safety monitoring but this doesn't necessarily mean that every trial needs a formal committee that's external to the trial organizers and to the investigators. One could, for example, in nonconfirmatory studies imagine an independent safety monitor who would essentially in real time evaluate the safety considerations of each and every patient in the study.

So what I'd like to do now is present an outline of the other times when one should consider a data monitoring committee and there are essentially three main bullets here. The first is risk to trial participants and this is the first and foremost situation that one wants to consider for data monitoring committees. The important thing is to be able to protect the subjects by insulating the decisions about continuing or curtailing the trial from those that may have a financial interest or even a scientific interest in the trial's success.

More generally, the overall welfare of patients with the disease and others in future clinical trials is

also a consideration for the data monitoring committee. The implication here is that if one had a failed clinical trial, that might stymie the development of an entirely new technology completely.

There are pragmatic issues having to do with the practicality of the data monitoring committee and its review and I'll go into each of these in great detail.

The third point is the assurance of scientific validity. There's a major advantage for data monitoring committees in terms of safeguarding the scientific validity of the trial and so without that independence, there may be a perception that the trial was not conducted in a scientifically valid manner.

So let's turn attention to the first of these three points, the first and foremost, that of protecting trial participants from risk.

A first and major factor to consider here is what is the end point, primary or secondary? Is it, in fact, mortality or major morbidity? If the answer to that question is yes, then a data monitoring committee should be considered very seriously.

And there are lots of examples where this could arise. For example, in a randomized clinical trial for a cancer chemo prevention strategy, one would consider strongly a data monitoring committee. In cardiovascular

device randomized clinical trials one of the major end points is called MACE. It's the major adverse cardiac events and that's, of course, either mortality or MI or future reoperation. Those are major mortality/morbidity end points and a data monitoring committee should be in effect there.

One could also imagine a randomized clinical trial for a new retroviral therapy for HIV and as a fourth example, a randomized clinical trial for a new regimen for adjuvant treatment of colon cancer.

So here are four examples where the primary end point is mortality or severe morbidity, major morbidity in a randomized clinical trial and a data monitoring committee is clearly indicated.

A second point is to answer the question would a favorable or unfavorable result early in the trial suggest termination? So this is an ethical question. If you're a manufacturer of some medical product and your product performs in an extremely optimal fashion, you and your investigators may be no longer having equipoise. You may want to stop that trial right away, rather than expose subjects in the control arm to the inferior therapy.

And that goes actually in the other direction, as well. If it turns out that the new product, be it a device or a pharmaceutical drug or biologics, if there is some

disadvantage in the trial that shows up early, for the safety of future patients in that trial you would want to discontinue enrollment for ethical reasons.

A third question to ask in this section about risk to trial participants is is the new treatment so novel that there is very little prior information on its clinical safety? For example, one might have a new molecular entity for which there is not any information in the confirmatory setting about its safety, for example. Then a data monitoring committee should be strongly considered.

Another example would be a medical device, a novel technology for which its operation is poorly understood. It's not clear to everyone exactly how the device might appear to be delivering benefit. In those situations a data monitoring committee should be considered seriously.

And a fourth question here is is there a particular safety concern? Has some safety concern already shown up perhaps in phase II trials that might cause one to look carefully in the confirmatory study? For example, perhaps there's a hint that there might be a liver toxicity problem. In those cases it would be well advised to have a data monitoring committee to follow up.

The fifth point is the fragility of the population that's being studied. If, for example, one is

looking at a trial that involves children, then data monitoring committees should be something that one considers. For example, in vaccines one might have a childhood vaccine trial. In those cases why would you worry about in particular a data monitoring committee? Well, one point has to do with informed consent. In situations where the population is fragile, the issue about informed consent would be of concern and it's something that data monitoring committees can help to safeguard.

The second point, the elderly, there are certainly lots of studies where the therapies involved are for the elderly population, who may not be well equipped to make decisions.

A third fragile population are patients in very ill health; for example, patients with HIV entered into a randomized clinical trial. In those cases a data monitoring committee is indicated. In a study for congestive heart failure where you're talking about people with severe disease, NYHA class three or four, again data monitoring committees would be a very good idea.

Are there adverse events that are expected or likely? These are sometimes difficult to protect. It may be difficult to anticipate in advance what's expected and what's unexpected but a data monitoring committee can help

safeguard these, as well as unanticipated or unexpected events that might occur.

And the last point in this section on risk to trial participants, are the participants at an elevated risk of mortality, major morbidity or toxicity? For example, in a confirmatory phase III drug trial, there might be the potential for severe liver toxicity. In those cases one might strongly consider a data monitoring committee.

If one were looking at an earlier phase trial having to do with dose finding in the case of a drug, one might consider a data monitoring committee there, as well, particularly if liver toxicity is something of worry.

Okay, so that's the first point. Let me go on now to the practicality of the clinical trials and data monitoring committees. The first point here has to do with the time lag. It could be that if a data monitoring committee is set up that the trial is so swift in its enrollment, so swift in the follow-up with the patients that the monitoring committee doesn't have anything to do; the study's over before the monitoring committee could even meet. In those cases it's not clear that a monitoring committee adds any value at all.

Now what one might want to do in cases where it's possible to enroll very fast is to stage the enrollment so

that that does not necessarily happen, to allow the monitoring committee to be able to look at what's happening over the course of the trial.

There are examples where the enrolment is very fast but the follow-up on the individuals is not. For example, in a vaccine trial, people can be vaccinated very quickly but the follow-up may take years before the evaluation of whether that vaccine is effective or not and safe can be done. In those cases one should consider a data monitoring committee not because you're going to stop future patients from enrolling in the trial but if you, for example, stop early that vaccine trial, you may be able to switch people over from the control arm to the vaccine arm. You may be able to allow the product into the public arena much more quickly. So this is an example where even though you can enroll people right away, there are still advantages to a data monitoring committee in terms of early stopping.

Is the trial large? If the trial tends to be large, then that's certainly a suggestion that a monitoring committee might be used. And certainly the tradition of clinical trials, if you go back in terms of the history of DMCs, the NIH trials tended to be quite large; the trials for the Department of Veterans Affairs tend to be large, as well.

If one has small trials it's not so clear. One could imagine that you're doing a relatively moderately sized trial but the implications in terms of the population that would be affected by the therapy could be quite large, in which case you might want to consider a monitoring committee nonetheless.

If the trial multi-centered? Is it a multi-centered randomized clinical trial? If the trial were only to involve a single institution it may be that the IRB could serve many of the roles that a data monitoring committee would ordinarily do. But most of the confirmatory trials that are submitted to the FDA are multi-center ones, so the conduct of these kinds of trials is much more complex and in those cases a data monitoring committee can be quite helpful.

Another point here has to do with globalization and the fact that there are now multinational clinical trials and this is so because not only is there the ICH effort for pharmaceutical products and biological products but there's also for medical devices a global harmonization effort, as well. If one has a multinational trial that's multi-centered, there are additional issues for monitoring committees that may have different implications for the different regulatory bodies that might be affected.

So, for example, if some of the centers are in the United States and it's being used as a confirmatory trial for the U.S. FDA, there may be some issues about whether the data shows safety and efficacy or safety and effectiveness for the U.S. part of the study.

Is the trial conducted over a long period of time? As we know, over a long period of time the practice of medicine can change; new therapies can be introduced. A DMC can provide some element of insurance for long trials because, as I'll talk about in a little while, there are changes that DMCs can easily effect that are much harder to manage if one would not have the data monitoring committee.

More points on the practicality of the trial. Could the enrollment of investigators or subjects be a problem? In some trials enrollment may not occur as one might plan. In those cases it may be possible that the data monitoring committee, in conjunction with the steering committee, may be able to make some suggestions of how to improve enrollment. There may be some inclusion/exclusion criteria that need to be contemplated for a change. And changes, I'll talk about later.

The whole issue about equipoise in terms of the ethical nature of the trial may be a problem for some of the investigators. Investigators may drop out as a source of new subjects not because necessarily anything from the

trial has been released, because presumably the trial might be masked or blinded, but things may have changed over time and they may no longer feel comfortable as individuals in terms of equipoise.

If the trial is not blinded, if it's not a masked trial, and this happens sometimes in medical devices, then equipoise can be, in fact, more of a problem because different investigators may have some impressions that they've built up over the conduct of the trial.

Can the sponsor afford to have a data monitoring committee or could they afford not to? Data monitoring committees are somewhat expensive. There's an issue about who pays. In the case of industry-sponsored trials it's usually the companies.

And the last point, and this really goes to the question of do we need data monitoring committees for every trial that comes to the FDA; if that were the case, we'd run out very quickly of well qualified individuals to serve on these monitoring committees. There simply aren't enough. Although there are lots of experts in this room, there are many, many more trials than there are experts.

More, of course, can be trained and there are issues about how to effectively do that but there are not enough, I suspect, experts for all the scientifically important questions that come up.

Okay, the third major point has to do with the assurance of scientific validity. A first question to ask is is it important that the perception of independence of the sponsor from the trial be preserved?

Now this afternoon Dr. Jay Siegel will talk in greater detail about the whole issue about independence and data monitoring committees but at least for now the whole issue about scientific preservation of validity can be helped to be ensured by employing a body that is independent of the sponsor and independent of the company, that doesn't have some vested financial and/or scientific interest in the trial. And this has advantages, of course, in terms of ethical behavior, as well, and the perception of ethical behavior.

Would the scientific validity of the trial be questioned without a data monitoring committee? And that's related to the point that I just made; namely, that if there were financial ties by the people who served on the data monitoring committee, that could create difficulties.

A third question to ask in terms of the assurance of scientific validity is is the interim analysis contemplated with the probability of stopping early for success or failure? As an example, there was a medical device that came on the scene in the 1980s called ECMO, which stands for extracorporal membrane oxygenation, and

this is a treatment for newborns, neonates, who are in some respiratory distress and if those trials were conducted now it would be very clear that one would want to have a data monitoring committee not only for the ethical nature of it but also to preserve the scientific validity.

What tended to happen was there were a number of trials that were done. There were different ways of randomizing babies to the two arms. One was the ECMO arm; one was the standard of care arm. And interim analysis played a key role in deciding when to stop those trials.

Another example when one would want to stop early and preserve the scientific validity has to do with an indication of a mortality advantage. So, for example, if the new product has some survival advantage, one would want to stop early but still be able to preserve the scientific validity. A data monitoring committee enables you to be able to have your cake and eat it, too.

And the last point on this slide has to do with the statistical analysis. In stopping early, in particular, there are lots of statistical issues that come up having to do with bias and without a data monitoring committee it's much more difficult to consider how to handle those.

In addition, in medical devices in particular, there are situations that sometimes come up where a company

comes in early for what was a fixed size trial and the suspicious person might ask well, why did they come in early? Were they continually monitoring the trial, even though that wasn't part of the plan? Those create nontrivial statistical implications in terms of trying to figure out how valid scientifically are the results.

The fifth point in terms of assurance of scientific validity is that during the trial is it possible that another study might be released that could compromise the trial? There may be well known other studies that are going on at the time that the trial is being conducted that may have implications in terms of the control arm or in terms of the treatment arm in the current trial and the release of information on these other trials could have grave implications in terms of the conduct of the trial and a data monitoring committee can help buffer that and provide, in the case of independent data monitoring committees, provide decisions of what to do in those cases.

There's an example of a device, for example, that's used now in stenting that has recently been approved by the FDA which allows for distal protection or embolic protection and the approval of this device has probably had implications in terms of other devices that are currently in clinical trials.

And the last point here is modifications to the trial. It's possible during the trial that different kinds of things could happen. A clinical trial, after all, is not a fixed quantity. It's almost like a living thing. It evolves; it changes; it can change. One of the obvious ways in which a clinical trial might need to be modified has to do with the sample size. When the sample size is calculated, different things are assumed about the rate in the control arm, the rate in the treatment arm. Those assumptions may or may not be valid and it may turn out that the trial is underpowered and the sample size needs to be adjusted. A data monitoring committee, although it's not easy, can grapple with this. If it's left only to a sponsor it creates difficulties. There are questions about the scientific validity in those cases.

A similar discussion can be made for changes to the primary end point. This has to be done with great, great care and I should hasten to add that when these sorts of changes to the protocol are made, it is extremely important that the FDA be informed about those changes and different products have different schedules that require the notification thereof.

It could be that the inclusion/exclusion criteria might be changed during the trial. There might be issues that the monitoring committee sees during the course of the

trial that are red flags. It could be that there are some enrollment difficulties and without a data monitoring committee it might be extremely difficult for a sponsor to be able to make the case about changing the end point or changing the inclusion/exclusion criteria on the fly.

It could be possible, in fact, that a trial design could be modified. For example, dropping an arm in a three-arm trial might be something that could be considered by a monitoring committee. In the case of medical devices it's not unheard of that during the course of the trial the device needs to be modified because of some problem that might have arisen and how do you do that? Without a data monitoring committee it's much more difficult.

So in conclusion, what I guess I would say is that for significant risk products, be they pharmaceutical drugs, biologics or medical devices, it's extremely important that companies and their sponsors come to the FDA and talk with the respective center, either the Center for Drugs, the Center for Biologics, or the Center for Devices and Radiological Health, at the planning stage. So if you have an IND or in the case of a medical device it's called an IDE, an investigational device exemption, come early, come even at the pre-IDE stage or the pre-IND stage and

have a conversation about data monitoring committees and get the best advice that you can.

The ultimate decision about whether to employ a data monitoring committee or not is a complex one and the unique aspects of the particular medical product and where it fits in the plan study need to be taken into account in the determination of this very complicated issue about when do you need a DMC and when you don't. Thank you very much.

DR. LEPAY: Greg, thank you very much.

With that, we're going to take our first break of the morning and resume at 10:30 with our first panel discussion. Thank you.

[Recess.]

DR. LEPAY: Again can I have everyone's attention so that we can resume with the panel? Very good.

I'd like to introduce our distinguished panel this morning, the first of our three panels today. Starting on my left first is Edward Connor, senior vice president for clinical development at MedImmune, Incorporated. Dr. Rick Ferris, director of the Division of Epidemiology and Clinical Research at the National Eye Institute at NIH. William Henderson, director of the Hines Cooperative Studies Program Coordinating Center at the Hines VA Hospital, Department of Veterans Affairs. LeRoy Walters, senior research scholar at the Kennedy Institute

of Ethics, Georgetown University. And Janet Wittes, president of Statistics Collaborative, Incorporated.

Again, as I said, a major focal point of this particular meeting is to get discussion, public discussion, as well as panel discussion. We're going to first then move into our panel and what I'd like to do is I'd like to invite each of our panelists to perhaps provide some of their own perspective, some of their own experiences in a few minutes. Then from there we can move more broadly into comments across the panel.

With that, I think we'll just go in the order I had mentioned here, starting with Dr. Connor.

DR. CONNOR: Thank you. I'd just like to make a couple of brief comments by way of background and experience. I guess I've been involved with various aspects of DSMBs or DMBs for the last 15 years or so through a variety of experiences, the first of which involved as a committee chair and protocol chair for some of the AIDS clinical trials group studies that were conducted over the past decade or so; as a committee chair involved in a portfolio of studies that interacted regularly with NIH's DSMB.

And as a protocol chair for 076, which was a trial of perinatal transmission using AZT, as a protocol chair involved in the conduct of that trial and ultimately

with the DSMB as a decision-maker, having been on the receiving end of the DSMB's decision to stop that trial early because of efficacy, first-hand was able to demonstrate the actual immediate impact of having such committees involved in certainly high-profile and important clinical trials. In those instances the rapid decision of efficacy in the studies allowed immediate implementation actually of that prophylactic regimen and had substantial public health benefit that was able to be facilitated through the intimate involvement with the DSMB.

For the last eight years or so I've been involved in the sponsor side as a clinical development person at MedImmune and in that capacity have obviously been involved in several instances of the development of large phase III clinical trials and have been involved in implementing and managing DSMB activities related to those trials.

So I think in general, the document that has been produced as guidance has really done a very good job at being able to capture the issues related to the implementation of DSMBs within clinical studies and by and large represents the paradigm by which decision-making is arrived at regarding how those agencies are actually involved in clinical development.

I think some of the issues that we'll ultimately be discussing have to do with the resource of folks who are

expert in those areas and how that resource can be efficiently used to optimize involvement in the major trials and also in some of the issues related to how you take the trials that don't necessarily fit into the clearly needing SMC or DMB or clearly not needing a DMB and make decisions around those issues. So that's all. Thank you.

DR. LEPAY: Dr. Ferris?

DR. FERRIS: In 1973 I had the privilege of my first data monitoring committee chaired by Jerry Cornfield and in the succeeding years I've been on a number and as time has gone on I'm more and more convinced of the value of these from a number of perspectives. Most importantly, rarely--never are we dealing with a perfect experiment and rarely do you find that everyone looks at the accumulating data and comes to the same decision.

I think one of the most important reasons for having the data monitoring committees, as was discussed earlier today, is these are living things and it takes a group of people to develop a consensus. The FDA often has panels to review data because these aren't perfect data. There's always missing data, there's always bias, so there's always interpretation of the results and I think the committees are important.

To that end, at the National Eye Institute now all of our interventional studies have data monitoring

committee review and I think it's important to note the differences that were pointed out earlier today between IRB review and data monitoring review. I don't think IRBs have the kind of expertise that is outlined in the document for reviewing accumulating data in a way that data monitoring committees do.

So at the National Eye Institute now all of our studies have on-going review. The intermural trials have one data monitoring committee. Many of the studies are very small. The committee probably reviews more than 20 different studies. They meet regularly but also have conference calls, interim conference calls, and when something comes up they review it.

Just one anecdote. I was reminded as I listen today, years ago a friend of mine in the Cancer Institute was talking to me about what he considered to be a very difficult situation. He was a statistician. He was looking at on-going accumulating data and noticed that there seemed to be more deaths than in the untreated group and he felt very concerned about noticing this difference. He talked to the investigator and as a clinician, we're all pretty adept at coming up with reasons why this person had this bad event or that person did and I think having this independent review is really an important part of clinical research.

DR. LEPAY: Thank you. Dr. Henderson?

DR. HENDERSON: I found the guidance document to be very well written, very well done, and I'd like to congratulate the authors. I think Greg Campbell did an excellent job this morning of pointing out the aspects and determining whether or not a data monitoring committee should be established.

Just a little bit about the VA. The VA is a very large health care system in the country. We do many different types of trials--drug trials, device trials, surgical trials, and lately we've been getting into trials dealing with health care organizations where the unit of randomization is not the patient but it might be the physician or the clinic or the hospital.

I found this document to be a very good exercise for me because it's just standard in our program that every one of our trials has a data monitoring committee. So I ask himself, why is this so? Are there some trials where we might not need it? And what are the reasons why we have a data monitoring committee for every trial? I mean we have some trials where the risk is not very great, like it's just symptomatic relief for the patient, but we still have a data monitoring committee and I came up with these reasons.

We do large-scale trials, multi-centered trials, mostly long-term trials. We have a vulnerable population that we're dealing with. But I think another very important reason, which is the third point that Greg Campbell brought up, and that is the scientific validity of the trial. I think an independent data monitoring committee gives the trial better credibility than if you don't have ont.

One other thing I wanted to just raise and that is the perspective of the patient. I've been the head of a coordinating center doing these clinical trials for 25 years and I've always asked myself, would I participate in this trial that we're doing? I think the patient deserves protection and I think the data monitoring committee gives some of that protection to the patient in terms of having an independent body reviewing that trial.

So I would argue that most trials should have data monitoring committees, even the small trials. You can combine the small trials and have one committee review several trials if you have small trials but I would argue in terms of having a data monitoring committee in most instances.

I think it's also important to, in every protocol, to specify that you've thought about the data monitoring committee, whether or not it's needed, if it

isn't needed, the reasons why, if it is needed, standard operating procedures, and so forth.

I agree with the other comments that data monitoring committees have been extremely valuable in our program and I would highly recommend them.

DR. LEPAY: Thank you. Dr. Walters?

DR. WALTERS: I, too, would like to commend the FDA and in particular, Susan Ellenberg for this very thoughtful guidance document.

I'd like to make three points in my comments. The first is that there's a gaping hole in the document as it stands and it begins with the title of the document. All of the focus is on the role of data monitoring committees and nothing is said in the title about the role of statisticians or coordinating centers and I think that these two groups, or in some cases it's an individual statistician, are equal partners and equally important partners in the monitoring of clinical trials.

In fact, I'd go a step further and say that the data monitoring committee meets quarterly or perhaps twice a year, takes a look at the data each time and renders a judgment. In an emergency the committee can be convened in person or by conference call but the individual or the group that's in the trenches day after day is the

coordinating center or the statistician or statisticians responsible for the trial.

So I would like to see the role of the statisticians included in the title. I'd like to add "and the role of trial statisticians" to the title of the document. In part 3 of the document where it talks about DMCs and other oversight groups I'd like to take out "oversight" and just talk about the DMCs and other groups or individuals and include a separate section on statisticians or coordinating centers.

Secondly, if statisticians or coordinating centers have such an important role in studies then everything that's said in this document about the independence of data monitoring committees I think should apply equally to statisticians or coordinating centers. If the trial is going to be viewed as having integrity then the statisticians have to have independence and an insulation from the sponsors. I think Section 6 in this document on the importance of the independence of the data monitoring committees is an eloquent section of the document and I would like to see something similar said about these important statisticians or coordinating centers.

And third and finally, I'll say something about the composition of the data monitoring committees. Here

I'm cheating a bit because we're supposed to only focus on parts 1 through 3 of the document.

Early in part 4 there's something said about the importance of having clinicians and biostatisticians on data monitoring committees. This is not simply an attempt to drum up jobs for people trained in ethics. I actually think it's very important to have an additional perspective on data monitoring committees; that is, one that complements the perspective of clinicians and biostatisticians. It may be a person formally trained in ethics. It may be somebody trained in law, as long as the person is not too adversarial. It may also be a consumer representative. But what I'm really interested in is broadening the viewpoint of the data monitoring committee and it's a kind of triangulation in a nonpolitical sense within the committee, to make sure that all important points of view are being heard.

I'll use an example from a recent DMC experience. Having someone from a Caribbean country in which a clinical trial was being conducted gave the data monitoring committee insights and points of view that we North Americans would never have had.

So the composition of the committee should be looked at carefully and I think in addition to clinicians

and biostatisticians, it might be very useful to have one or two additional perspectives.

DR. LEPAY: Thank you. Dr. Wittes?

DR. WITTES: I'd like to echo the congratulations that everybody has made about the guidance document. I think that it struck really the right tone, that as a first guidance it's come out in a very flexible way addressing a lot of the issues and I think we'll all be fleshing out how it gets implemented over time.

I want to thank LeRoy for his very eloquent support of statisticians and also to comment that I, over the years, have found how useful it has been to have ethicists--and actually I like them trained in ethics--on the committees because they do bring a very, very different kind of orientation and perspective that I think is very useful.

I'd like to tell you a little bit about how I started in DSMBs or DMCs--I will try my best to change the initials--and then to argue for some training, which I think Greg alluded to but I want to emphasize.

My first experience was at NHLBI. I came in in 1983 and like the first day I was there Gordon Land, who's here, and Kent Bailey--I don't know if Kent is here--came up to me and he said, "Look, just go to every DMC"--then it was DSMB--"every DSMB that you can go to because you can

learn a lot, it's the only way you're going to understand it and it's really fun."

So I did that. Now, of course, unfortunately in these days we can't do that anymore because now there's many more rules about who can attend and who cannot attend, but it provided for us at the Biostat Branch, for the Biostatistics Branch at NHLBI, the ability to go to committees to really understand--and I echo what Rick said--the fact that these decisions and the discussions are very complicated, they're very nuanced, and they reflect a certain sociology of a committee that varies from committee to committee.

And I would contend, and this is leading into the training, that if one plops a statistician onto a committee as the first time that person has ever been on a committee or one plops an ethicist or one plops in a clinician, although there's usually some other clinicians on the committee, it can actually be very harmful because the person is learning and training at the same time, learning him or herself and training the committee in statistical or ethical principles for DSMBs for the first time.

I do think that topic number two, the guidance talks a lot about the similarities between government and industry trials and roles of DMBs in the two and I've been vacillating over the months that I've thought about this

but I've come to believe that there is actually a profound difference in the way in which these two sets of trials are run, that government trials, as several people here on the panel from either NIH or Bill from the VA, that they are really spending public money and they're sponsored by the public and there is a sort of public trust that I think is fundamentally different from an industry-sponsored trial and I think we do have to think about how that translates into what roles of DMBs, and it'll come out, I guess, in the afternoon, who attends.

The other issue I did want to raise, I have to respectfully disagree with Greg on his extension of the roles of DMC to recommending changes in certain aspects of protocol. And again I vacillate about this. I think it's very important to have flexible designs for trials but I think that a data monitoring committee--remember a data monitoring committee is seeing data on efficacy and for it to have the ability and the right to change end points and to change crucial aspects of design I think can sacrifice the integrity of the design. I think we have to think very clearly about who is responsible for that and whether that's a DMC role or not. Thank you.

DR. LEPAY: Thank you.

I'd like to open this up now among the panel for any additional comments or questions, information, they could provide us with. So again any takers?

DR. CONNOR: I'd like to just follow up a little bit on what Janet said about training and the composition of the DSMB or DMBs. One of the things that happens during the years that I've been on the industry side of this is that obviously when you're approaching a phase III trial and a lot has gone into the development of a particular product you're in many ways handing over to this independent group a lot of very profound decisions. That obviously is true in the public sector, also.

But the talent base of folks who understand the role of the DSMB and the decision-making of the DSMB is really very critical and in all the instances that I've been involved with so far, we've been very lucky in the sense that both on the NIAD side and on the private industry side we've been able to have folks that are very talented and experienced involved in that process but I can imagine that there are instances where, as more safety monitoring committees are charged and more large clinical trials get done, the need for folks specifically experienced and mentored in the process of DMC activities is really very critical and the confidence with which folks are able to invest the responsibilities into the groups is

very importantly based on the talent base that exists to be able to accomplish those goals.

So somehow as we implement this very important process more broadly than we have it right now, it's very important that an element of specific attention be paid to the development of folks with specific expertise in this area.

DR. FERRIS: I'd just like to follow up on that with regard to clinicians on data monitoring committees because it's clearly important to have that perspective.

One of the problems that I've seen over the years with clinicians on data monitoring committees is by nature we're interested in individuals and what happens to this individual and at times some of the clinicians have asked literally for every case report. Bring in the wheel barrows because they want to see every last piece of data.

I think it's important to have all perspectives but among the clinicians I think there has to be at least one who is experienced in clinical trials and clinical research so that the committee doesn't start down the wrong path.

DR. HENDERSON: I thought Janet raised a very interesting point and that is the trials at NIH and VA are government-sponsored, whereas the industry trials are sponsored by industry, funded by industry, and what

implications does that have on the need for data monitoring committees or the operation of data monitoring committees? Did you have something in mind by your comment?

DR. WITTES: No. My comment was just that my goodness, they're different and that we need to think about--it's actually been precipitated by some issues where some of the institutes want to be in closed sessions of committees and some of them do not. Certainly in industry-sponsored trials--well, I shouldn't say certainly--I think the standard is not to be there.

So I've been actually struggling in my own mind about whether the same model should apply and whether it is ripe or not ripe for government sponsors--and whether the word is sponsor or not, I don't know--to be in closed sessions. So I don't have an answer but I do think the thinking needs to be different.

How's that as a cop-out answer?

DR. HENDERSON: But it seems to me that I think in the document they made reference to the independence of the data monitoring committee and the fact that the industry is actually excluded from the discussion of the outcomes broken down by treatment group or they aren't involved in the data monitoring committee at all, and that's the definition of independence.

It seems to me that in any case I think the independence is good but basically the data monitoring committee makes recommendations back to the sponsor and then it's the sponsor's job to act on that. They might act on it; they might not act on it. So the industry sponsor has the last word on those issues.

One question that was raised in my mind, what if there is a conflict between what the data monitoring committee recommends and what the sponsor wants to do? How is something like that resolved? Maybe that'll come up later on in operational issues.

DR. WITTES: I think what Bill raises is exactly the issue that I've been struggling with. If a committee comes and recommends to the sponsor, either the government or the industry sponsor, to make such-and-such a change, I think the tradition has been for such an industry recommendation the industry ought to make that change and the committee may not say why it's making the recommendation. It just says make this change or let me see these data or let us see these data, or so forth. Whereas when such a recommendation goes to a government sponsor it is very hard to not give the information that's leading to the recommendation and it's very hard to expect that somebody responsible for public monies is going to make changes without justifications.

DR. ELLENBERG: I just wanted to respond to a comment that Janet had made earlier about the role of the data monitoring committee in making protocol changes. I just wanted to clarify that we certainly agree that when a group has seen interim comparative data they're not in the best situation to make a recommendation on a change that could, in fact, be impacted by the data that they've seen. But the fact of having a data monitoring committee monitoring the trial actually frees up the trial leadership to make changes because there may be a need to make a change in a trial. Sometimes it comes from external information that comes out and if the only people who are in a position to make the change are people who have seen the interim data, you have no way out of this sort of conundrum. But if the data monitoring committee is reviewing the interim data, then that will free up the trial leadership to be able to make a change that they think is needed.

So our intent is not that the data monitoring committee would, in fact, be recommending a change in a protocol end point. It's that they protect the ability of the trial to make such changes.

DR. FERRIS: I'd like to just address the issue of whether the government and industry are the same. I think we can probably all agree that they're not and there

are certainly perceived differences between how the trial comes out and how the government wants their trials to come out and how industry wants their trials to come out. I think we all want them to come out successfully but a lot of the trials I've been in, I would have been equally happy if we showed the treatment didn't work. So there is a difference.

However, I think it's important to remember that data monitoring committees aren't always correct. I was listening to the historical issue of the University Group Diabetes Project and I was thinking that based on UKPDS results, maybe the first data monitoring committee made a mistake.

I think there are times where the decisions from a data monitoring committee need review and I know at National Eye Institute a number of times we've either had ad hoc or in-place review committees review the data monitoring committee's assessment and there have always been times when the data monitoring committee is not unanimous. And a lot of data monitoring committee work--I think some of what Janet was talking about in terms of the training, they really are consensus development exercises as much as frequent statistician assessment of the data.

DR. ELLENBERG: We do recognize that government and industry trials are different. We do think, however,

that the issues that are raised can really apply to both types of sponsors. What that means in terms of implementation of approaches may differ but it does not mean--what Rick just said about sometimes data monitoring committees may make the wrong recommendations, I think that's true. I mean I think the strongest support of data monitoring committees would never say they're right 100 percent of the time, but that's true for data monitoring committees in industry trials just as well as data monitoring committees for government-sponsored trials.

So I think the fundamental issues are ones that all sponsors need to think about. That's really the main point.

DR. LEPAY: Dr. Walters?

DR. WALTERS: Janet Wittes's suggestions about training reminded me of another point that we might want to consider today and that is the role of empirical research on the actual functioning of data monitoring committees and perhaps evaluation research on how well they're functioning.

Perhaps that component ought to be built in right from the start of the FDA guidance so that 20 years from now the Office of Inspector General won't have to do an independent analysis and say oh, there's some deficiencies

in the way data monitoring committees function, as that office did for institutional review boards.

So some kind of periodic look at the composition of the bodies, how many members there are, how frequently they stop trials before the planned termination, might provide helpful feedback on how the whole enterprise is working.

DR. LEPAY: Dr. Wittes?

DR. WITTES: I'd like to distinguish two kinds of right decisions. This is in relation to Rick's comment. In light of data that come out later we can always learn that we've made a wrong decision and that can happen in science in many different ways and that's why we replicate experiments, because it's possible that one experiment shows one thing and one shows another thing.

I think the best we can hope for for data monitoring committees is that they act rationally and reasonably and develop good consensuses that other people can look back and say yes, confronted with these data, I, too--I being a reasonable person, also--would have made the same decision or I can't fault the process of the decision. But we can't assume that data later is going to confirm what we think we saw.

OPEN PUBLIC DISCUSSION

DR. LEPAY: Thank you.

I'd like to open this up now to the audience. What we'd like to do is focus our comments and focus attention in this particular section on the first three sections of the guidance document if at all possible, dealing particularly with the need for a DMC and the relative roles of DMCs and other groups that are involved in overseeing clinical trials.

So again I'd encourage people to step up to the microphone. Again these transcripts are being prepared and we'd appreciate it if you'd identify yourselves.

DR. LEVINE: Thank you. I'm Bob Levine. I'll have my opportunity to speak later but I want to make two quick points on what came up in this panel.

First, some people might leave this room thinking that LeRoy Walters and Janet Wittes made the same recommendation about having ethicists on the DMC. LeRoy though, when he spoke of ethicists, included people who are not trained in ethics and even included somebody whose only descriptor was that he or she came from the Caribbean. I think what LeRoy's trying to tell us is that we need a different perspective and it may be an ethicist; very commonly it would be.

I think the later comments that were made about people who are schooled and working on DMCs is extremely important. There are a lot of tyroethicists who can be

really very disruptive, thinking they're going to apply their principles in the field of clinical trials.

The other point I want to address is that there are indeed great differences between the DMCs in industry and in the government. I agree with Susan Ellenberg that they can all be expected to follow the same basic principles as set forth in this excellent document. However, they could learn from one another. Industry tends to have much greater formality in the contractual arrangements and much greater specification of such things as confidentiality rules and I think people on NIH DMCs could benefit by being reminded of that sort of thing. It's just assumed that everybody who serves on a government DMC already knows all about that and often most of them do.

I think government could also learn from industry about how much to pay a DMC member.

And my final point would be that one major difference, and this, I think, reflects what's been said about--I think Rick Ferris brought this up about the different ideas about what a satisfactory outcome would be--I think that we see that manifested in the industry's strong tendency to try to set the stopping rules or guidelines themselves, rather than let the DMC engage in its own exercise of establishing the stopping guidelines. And I think that there should be some discussion of that,

about who should set the stopping--I don't like stopping rules but stopping guidelines, and how to go about doing that. Thank you very much.

DR. LEPAY: Any comments from the panel? Okay.

MR. CONSTANTINO: Joe Constantino from the University of Pittsburgh Graduate School of Public Health. I'm also the associate director of a data coordinating center and I really came here today to reiterate Dr. Walters's comments. After I read the document it was very clear to me that there was a gaping hole in the document in terms of dealing with clinical trials, data coordinating centers and the role of a statistician of that coordinating center with the DMCs.

Having had over a decade worth of experience on dealing with independent data monitoring committees, it's clear to me that it's essential that the statistician who works with the data monitoring committee needs to be that statistician who's involved on a day-to-day basis with the data and who sees it in an unblinded fashion. He's the one that actually is monitoring the trial for safety and brings to the attention of the data monitoring committee things that occur.

To suggest that an individual who should be going to the data monitoring committee, as is done in the later portion of the document, should be totally independent of

the day-to-day operations is not in the best interest of the primary goal of a data monitoring committee, and that's safety of the participants.

The document doesn't deal enough with the interchange and the balance that we need to achieve between protecting the confidentiality of the data, the integrity of the trial, and protecting the participants in the trial. There is a big play-off of all of these things and this is where some of the differences between industry-sponsored and government-sponsored contracts come into play. There's differences there.

There's also differences that must be recognized that come into play in terms of people who actually sit on data monitoring committees aren't totally devoid of conflict of interest. These people participate in cooperative groups who are doing similar trials to the ones they're investigating. They go back to the universities and have colleagues who participate. So there are pressures on them to breach confidentiality but we accept those levels of breaches to protect the risk of the participants. This kind of balance of protection of the risk to participants versus the integrity of the trial needs to be stressed more in the document.

DR. LEPAY: Thank you. Any comments from the panel?

DR. WALTERS: Perhaps one of the reasons that the role of coordinating centers and statisticians is not accented more is that biostatisticians are very modest people. Even in a wonderful book like "Fundamentals of Clinical Trials," I would say that the role of statisticians in the conduct of clinical trials is, if anything, underplayed, even though this book was written by a group of very distinguished statisticians.

So FDA may accurately be reflecting what's in the literature. It may be that the biostatisticians are just too self-effacing.

DR. TEMPLE: Some of them perhaps.

Actually, I wanted to follow up on the same area that Dr. Walters raised. The obvious reason that the biostatistical center isn't covered is this was a document about data monitoring committees but you can see in the document considerable nervousness about who does the analysis.

One model is that somebody in industry, presumably very shielded from the corporate management and everything, analyses, the data, presents it to the committee, but that makes people a little nervous, as the document describes, because there are nonverbal signals and maybe you really reveal it.

So the alternative is a more or less independent statistical center. But nonetheless, I think the document continues to treat that center as more a creature of the sponsor, working for the sponsor, and I can tell you personally these centers vary considerably in whether they're really neutral or whether they're really advocates for the sponsor.

So for all those reasons, the document doesn't dwell on that very much but sort of accepts a wide range.

Now I'm wondering whether you and the other panelists think that we ought to be more insistent on saying at least for major outcome trials that the people who put the data together really ought to be arms-length from the sponsors. Is that what you're proposing? I couldn't quite tell but I think it needs more discussion.

DR. LEPAY: Comments? Yes, Dr. Walters?

DR. WALTERS: Yes, I do think that there should be independence of the individual or group collecting and analyzing the data by treatment arm and that what's said in this document about the importance of the independence of the data monitoring committee for the integrity of the data in the trial applies with equal force to the role of the statisticians that are analyzing the data.

DR. TEMPLE: Is it particular studies that need that treatment, all of them? You're basically describing a

situation in which drug companies no longer analyze their data, period. Is that what you're saying? Or is it only certain major studies with important outcomes where you feel that that was essential?

DR. WALTERS: I guess as a rule of thumb I would say that where there's a data monitoring committee there ought to be an independent statistical center or an independent statistician who serves the data monitoring committee.

DR. WITTES: I think there are several issues being conflated here. There's issues of confidentiality, there's issues of conflict of interest, and then there's issues of credibility. I think these are different. And I think they're going to come up this afternoon but it's important to keep them separate and it seems to me that each one of them, as you think of each one separately, it speaks to a different kind of model and the issue we have to face is how do you have one model that satisfies them all?

DR. FERRIS: I'd like to make one comment regarding this and that is when it comes to rules for data monitoring committees I'm not sure there should be any. There are probably a lot of ways of doing the job and I'm not sure any one fits all. I think saying that never can a company do its own statistical analysis seems to go too

far. If a company does do its own statistical analysis surely there will be skeptics and critics that are going to want to see that data and do the analysis another way. And I think we all realize that the data monitoring committee is beholden to the coordinating center and statistician. A lot of mischief can happen between the data and the data monitoring committee, so having good, competent people is the key. And, in the end, fudging the data is going to wind up being detrimental to everybody.

DR. LEPAY: I'll go to the speaker at the microphone.

ATTENDEE: Actually, I think I'll yield to the ones in front of me because I have a feeling they want to talk about the same vein and I want to take another one.

ATTENDEE: Just a follow-up on the point that was raised a little bit earlier. It is important for the data monitoring committee to deal with a biostatistical center which is also independent but there are levels of perceived independentness. Clearly a statistician who's working for a private research group around the beltway is different than one that's working for an academic-based clinical coordinating center. It's different than one that might be a private consultant working for an industry.

These are the types of things that need to be recognized as differences between the types of trials. And

when I said there's a give and take between--an arm's length is an arm's length but it might be a two-foot arm or a three-foot arm and sometimes a two-foot arm is acceptable. These are the kinds of things that I think need to be brought out and made clear.

DR. ELLENBERG: Could I just ask for you to elaborate on the difference between, say, a coordinating center at an academic organization and one that's a private consulting group?

ATTENDEE: Sure. An individual who's working at an academic center has his primary boss as the university. He's a tenured person at the university. His job doesn't depend on whether or not, in a real sense, whether or not this trial turns out one way or the other.

So in a perceived sense--maybe it's not true in reality but in a perceived sense he's going to have "less of a conflict of interest" than somebody who works for a private company who makes their whole living by doing these kinds of things for industry or specifically for an industry group panel set up to do the analyses.

So these are all perceived levels of independentness that need to be weighed plus and minus against how far does the perception have to go to protect the integrity of the trial? That's the kind of thinking that I think is still missing in this document.

ATTENDEE: I reserve the right to go back to my original point but I can't let that one go. I think that you've gone too far. It's absolutely not true that everyone at an academic institution is not beholden to the sponsor.

ATTENDEE: I said perception. I didn't say reality.

ATTENDEE: But the reality is important. I mean many people are totally dependent on the grants or contracts from NIH or industry for their job and they don't have a paycheck if that contract ends for whatever reason. So I think we do have to be careful here.

Also, I think there is both a real and perceived difference between coordinating centers who are sponsored by the NIH and coordinating centers who are sponsored by government--I'm sorry, by industry. At NIH it's virtually impossible to have more than a two-inch length from the sponsor to the coordinating center. They hold the contract. In many instances, if not all, they actually interact quite closely with the DMC and the coordinating center. They also see the unmasked data, whereas in most industry studies, at least that I have some responsibility or interaction with, they're more like at a one-mile length as far as the blinded data. At least that's the way it's perceived. I'm not sure about the reality all the time.

I do want to say something else but I'll let Dave talk for a minute.

DR. CONNOR: I think a lot of the issues related to industry trials--and while I don't represent industry I do have some experience in doing that over the last couple of years--is that obviously the outcome, the desired outcome is approval of a drug and the ultimate arbiter of that is really going to be very dependent on that arm's length decision.

So a lot of effort gets put into really assuring that we're as separate from that decision as possible so that, in fact, at the end of the day the integrity of the trial is maintained.

So I think there's a lot of effort on the industry side, as folks have pointed out, to be sure that the arm's length is several arm's lengths away and how that gets accomplished is obviously dependent on the organization. In some organizations it may be eons away where the analysis gets done, rather than the corporate decision-makers are and in other places which are small organizations like ourselves, we really depend on the independence of separate organizations to do those analyses because it is a smaller kind of organization.

DR. LEPAY: You had another question?

DR. DeMETS: Dave DeMets, University of Wisconsin. I have two points: one on IRBs and one on training.

I'm not sure what the ultimate responsibility of IRBs will be but I'm pretty convinced as of right now that IRBs are not in a position to do much monitoring, as we're talking about here. The composition, the resources, the talent just isn't there. And while we may want them to do certain things about monitoring local studies, the fact is they can't do it and it would be a terrible disservice to patients and investigators if we dump that responsibility onto IRBs without a substantial investment in those IRBs. IRBs have had enough trouble meeting the paper requirements, as we've learned recently, but to ask them to do the other, do additional without substantial increases of resources and talents would be a recipe for disaster.

The second point, on training, I have to take an opportunity to put another plug in. Some wag said that this document is a full employment act for statisticians. The current situation before today might be that we already are desperately short of a training pipeline of biostatisticians. Those of us who are in academic departments training biostatisticians know that students go out and get four and five job offers. When we try to recruit faculty we work at it for a long time.

So the pipeline is already short and if this process, which I strongly endorse and support, nevertheless, we have a double training problem. We have to train those we have but we have to step up the training process and right now there's no initiative in place to do that.

DR. LEPAY: Thank you.

MR. VERDA: Joel Verda, George Washington University. I almost yielded too much because Dave actually started along the lines that I was heading for.

My concern is that the document, although it's specific for DMCs, has opened the door for another issue and that is the IRBs. Over the last 50 years as clinical trials have developed we've seen developments in coordinating centers, in design, in monitoring, in DMCs going from occasional trials to almost all to almost all industry trials of the nature described this morning.

But in the last five or six years we started to see a trend that's a little disturbing and that relates to the IRBs' responsibilities. We, for example, recently have received two or three requests from IRBs for blinded data, saying that they can't do their job unless they see blinded data. I think someone, and I'm not sure who it is; I'm sure it's not this panel but the FDA, NIH, OHRP--somebody

has got to give these poor souls some guidelines, what they don't have to do and what they do have to do.

I certainly agree with Dave that it's impossible for a local IRB to become a DMC. In fact, it would be the death knell of any clinical trial if you had 12 or 160 IRBs trying to monitor the trial along with the DMC.

DR. LEPAY: Thank you. I was going to say I think that's an issue we're also going to take up this afternoon but certainly that's one of the major impetuses behind our discussions here today, is to come to reality with respect to the fact that there are certain responsibilities that need to be met in clinical trials and we need to look very carefully at where those can best be accomplished. And hopefully that is going to be one of the take-home messages at the end of the day, both for us and for those who will see this transcript.

If I could go to the next individual in the back?

DR. STUMP: Dave Stump from Human Genome Sciences. I'll have several comments to make in one of the afternoon panels but I did have one topic that I'd like to bring up and maybe elicit some comment from the panel. It has to do with when is a DMC needed?

In Dr. Campbell's presentation and in the guidance document it talks about a therapy that is so novel that there's very little information on clinical safety

that exists. This can actually be the case with many phase I trials, any new molecule first entering man. I'll argue that for novel biologics, something I actually live with day in and day out, you may often not have relevant preclinical data because of species specificity of human proteins.

Would it be the panel's view that phase I trials require DMCs and if DMCs are required do these need to be external DMCs? We actually get IRB requests now for multi-center phase I trials for external DMCs, which in my mind seem to supplant a great deal the relationship historically that has worked between the sponsor's medical monitor and the FDA's product reviewer, where a constant dialogue takes place with frequent safety monitoring of these trials, but it's becoming an issue certainly for those of us on the sponsor side and I'd love to hear some discussion about it.

DR. LEPAY: I'd like to go down the panel, if possible, and see if we have any comments. This is an issue that's certainly very pertinent to us in developing this guidance.

DR. CONNOR: I think a lot of the issues, some of the issues are addressed in the guidance document but are a little unclear as to the answer to that question. From our perspective, we are also in the position, similar to the last speaker, where more and more is being demanded of the

sponsor from the IRBs relative to separation and independence even early in clinical development, so much so that now very often the IRB will regularly request updated information, albeit blinded or unblinded, on a regular basis, demanding a lot of resource intensity to provide such information while the trial is actually on-going and, in addition to that, now actually making specific demands that there be an independent individual in early clinical safety monitoring committees even if the origin of those are actually internal.

I think we've debated a lot about the value of that, early on. The expectation is that there are specific reasons for such review; we've accommodated those reviews. And I think that it's important in other instances where there's not a specific safety concern or there's not an expectation that there's going to be the need for more broad review, we have tended to wait until the next set of trials, not the early dose escalation range-finding trials but the set of trials that's sort of the transition between early clinical development and phase III clinical development, which is where ideally most of the pertinent discussion resides.

DR. ELLENBERG: Before other people comment I just want to make a clarification that our intent in this document was not to suggest that a large majority of phase

I trials would require data monitoring committees. We think that there could be, on occasion, an early phase trial of something where there really were important safety concerns and where a set of people without any particular investment in the trial might provide some useful advice, but our intent is not to suggest that that would be typical or even frequent but rather, a rare occurrence but a possibility that we wanted to raise.

DR. FERRIS: I said earlier, and I echo what Joel said, that I think the responsibilities of the IRB and the responsibilities of data monitoring committees, although each have factors that are similar, the differences are important. And to that end, what we've done, and I think on an institutional basis it doesn't have to be an NIH institute but any institute that has an IRB, they may want to consider what we've done. That is we've formalized the relationship between our data monitoring review committee and the IRB.

I don't think--I said before I don't think there should maybe ever be rules, stopping guidelines; DSMC guidelines are appropriate. Independent review I think is important, of the data, and if the IRB works something out with whether it's a DSMC or some other independent reviewers, I think that's helpful to have in place so that whenever the study is--these are all intervention studies

I'm talking about now--is reviewed by the IRB, that there's a written document from some independent group saying we've looked at the data and at this point we don't see any evidence to modify the study.

DR. HENDERSON: We haven't had really any experience with phase I trials so I really can't comment on that.

I would like to make one comment about the IRB issue. We're also seeing the phenomenon of local IRBs in the VA system requesting unblinded data and what we've tried to do is we have a data monitoring committee reviewing each study and once the committee meets and decides on an action, we communicate that action in general terms back to the local IRBs because I think that many of these local IRBs aren't even aware that there's a central DMC reviewing the data, outcome data from that study. So we communicate back a general statement to them that these are the data monitoring board members, they reviewed the study on such-and-such a date and their overall recommendation was that it continue and there are no safety concerns, a general statement like that. Whether or not that's going to be adequate for the local boards, we've only been doing this for about six to 12 months so I'm not sure.

DR. WALTERS: The document deals with the question of independent safety monitoring on page 16 in 4.4.2 about early studies and I guess I would suggest that even in phase I studies, independent safety monitoring is really important and it's simply to guard against self-deception by the investigator who's trying out something new. It's another pair of eyes, just as a check. Very often it won't be a committee; it will just be another person within the same institution or the same company. But it provides a measure of safety for the participants even in phase I studies and it's something that IRBs simply are not equipped to do.

DR. WITTES: I actually think the question is backwards, that we shouldn't be asking whether phase I trials need DMCs but we should be asking what safety monitoring should be done for phase I trials.

I think the issues have come up because of at least three really unfortunate events--the liver toxicity death at NIH, the death at the University of Pennsylvania, the death at Hopkins--and I think that what it says to people is my goodness, maybe phase I trials are not being looked at in the way they ought to be. But I agree with LeRoy that the way that one can monitor trials for safety need not necessarily be a DMC.

My own personal experience being on DMCs for phase I trials is that we were singularly ineffective, that the trials go on, as Greg described, the trials can go on so quickly that the DMC doesn't function and that's really what happened to us in several trials.

So I think what has to happen is in a phase I trial of a novel entity there's got to be a really clear safety monitoring plan and we need to be very flexible about how it gets implemented.

DR. LEPAY: Thank you. I'd like to take each of the speakers who are currently at the microphone. I think I'll start on my left. Please identify yourself if you would.

MR. VENABLE: Tom Venable from Fujisawa Pharmaceuticals. I have a question about data coordinating centers, back to the arm's length or kind of a rock and an expensive hard place question.

Sponsors have to maintain the blind in-house, all right? That usually sets us on a model of doing the data coordinating center through a CRO. Will the guidelines emphasize that independence of data coordinating centers or will it invite the mechanisms to occur within a sponsor?

DR. ELLENBERG: We'll be dealing with that this in talks later on. We'll go into that in more detail.

DR. LEPAY: In the front?

MR. LEWIS: It seems like all three of us are Toms. Tom Lewis, RAND.

I'd like to get back, although the previous person did also, to the topic that vexes everyone in Statistics 1 and that is statistical independence, in this case independence of statisticians. I think the document is too vague on it because every DMC I've been on or every coordinating center I've been in, at least in the coordinating center role, we are totally collaborative with the investigators, that independence is not viable if you're going to be a statistical scientist, as opposed to one running the data.

But what's very important, and I think the document should focus more clearly on it, is independence in a certain role. It's that role of monitoring the study and preparing reports for the DMC and interacting with the DMC and with that kind of clarity I think it's a good concept. But the idea of just generally saying the statistical center or statisticians are independent of the sponsor is, in fact, promoting what is a very bad idea.

DR. FLEMING: Tom Fleming, University of Washington.

Janet in her comments appropriately emphasized the importance of experience in the people who would be on monitoring committees. At the same time it's been

acknowledged that these committees are much more broadly implemented. And Greg Campbell in his presentation, under the topic of practicality of DMC review, acknowledged then that one of the logical issues that follows is are there going to be adequate numbers of well qualified experts?

I think as we configure these DMCs we need to be thinking not only about today but about the future. And in configuring these committees to address Janet's issue of ensuring that there are people that can be available that are experienced, many of us have argued that we should be thinking about an apprentice approach where you intentionally select in your configuring these committees a combination of people with experience and without. So if you have two statisticians, for example, you try to bring in diversity, one with experience, one who really has important contributions but without the experience and they wish to gain that experience.

It is, in fact, an additional investment today but I think sponsors, both government sponsors, industry sponsors, and societies for clinical trials should be thinking carefully about this issue, about how can we work together to configure today's committees in ways, for example, through an apprentice-type approach, to broaden the population of experts who have the experience for future DMCs.

DR. LEPAY: Thank you.

I'd like to thank our panelists for their excellent contributions, to those members of the audience who provided additional comments, and we're going to move on to a discussion of the next section of the document. So if we could give a hand to our panelists.

[Applause.]

DR. LEPAY: Our next speaker is Mary Foulkes, deputy director of the Office of Biostatistics and Epidemiology in the Center for Biologics, and she's going to discuss the section of the guidance document dealing with DMC establishment and operations. Mary?

ESTABLISHMENT OF DMCs AND OPERATIONAL ISSUES

DR. FOULKES: Thank you very much, David.

After this morning's discussion I'm going to start by assuming that we've already addressed the question of whether or not a DMC is necessary and then ask the question what's next, what follows?

If there is to be a data monitoring committee it's generally one that is appointed by the sponsor. And by that I'm terming the sponsor as a very broad use of that term. If there is, in fact, an existing steering committee, the appointments to the data monitoring committee are usually mutually agreed upon between the steering committee and the sponsor. Sometimes the sponsor

delegates this responsibility, as has been mentioned already this morning. The DMC is also funded by the sponsor in the sense of covering expenses for the meeting, honoraria, et cetera.

And the specifics of the need to maintain some independence between the sponsor and the DMC, as we've already discussed a little bit this morning, will be discussed in much more detail after lunch by Jay Siegel.

There are multiple factors to be considered in the construction of a data monitoring committee. Not only does there have to be an agreement among those who are selecting and identifying the membership of this DMC; it needs to be multidisciplinary, as we have heard, and I'll talk a little bit more about that in a minute.

The size of the DMC is really a function, largely a function of the complexity, although we've just heard a few suggestions for expanding the size of the DMC, which certainly ought to be considered. Then the membership of the DMC have to be in general agreement with the clinical trial as it's proposed with the specific hypothesis that's to be addressed, with the design of the trial, and with the end point that's been chosen. And we've already touched on the issue of minimizing the overall conflict of interest.

To get back to the size of the DMC, the document does refer to an expected minimum size of three,

approximately three. There have been examples of smaller size DMCs but they have generally had some serious problems, so the recommendation is to have a committee of at least size three.

And as I was looking over my slides this morning I realized that I actually made this slide before LeRoy's comments earlier this morning. I would suggest that the areas of expertise that need to serve on a DMC are first of all, obviously the relevant specialty of clinical medicine that's appropriate for the given trial; the expertise in biostatistics that we've already heard about, and modesty prevents me from going further; the involvement of biomedical ethicists. As you can see, the top three are highlighted in yellow.

If your DMC is larger than size three you should consider involving some other specialties as a function of the characteristics of the trial. And also it has been mentioned earlier this morning the involvement of possibly a patient advocate, community representative. So these are the various persons that would be suggested as possibilities.

Then there are other issues to be considered when you're constructing your DMC. We've already touched a little bit upon geographic representation, representation of the relevant demographic characteristics, which comes

into play, for example, if you're dealing with a study that involves one segment of society versus another.

We've already also heard discussion of the involvement of individuals with prior DMC experience, which is very important.

The aspects of conflict of interest. I don't mean a very narrow definition of conflict of interest. Conflict of interest can involve lots of things. It can involve financial conflict of interest. Investigators enrolling in the clinical trial itself have a certain conflict of interest. Then there is a very broad category of intellectual conflict of interest. So this is not meant to be a very narrow aspect to be considered and all of these things need to be considered when you're constructing your DMC.

The other thing to be considered, which is a very important choice to make, is who is the individual who's going to serve as the DMC chair? In this context even in the situation we face right now with limited numbers of individuals with prior DMC experience, it really is important for the person who serves as the chair to have prior DMC experience. They also obviously have to have a very strong scientific background relative to the trial at hand. They have to have some appreciation for the

administrative issues because a lot of the recommendations from a DMC have administrative implications.

We've talked about consensus-building and being a facilitator. That is a very important skill that this individual must bring to the process. You'll see in a moment that their skills as a communicator are going to be called upon, so that needs to be considered.

And lastly, they really should be in a position to make a commitment for the duration of the trial. It's somewhat disruptive to have changes in the investigators involved in the trial in the middle, it's somewhat disruptive to have changes in the individuals participating in the DMC but it's very disruptive to have a change in the DMC chair. So this individual should be willing to commit for the duration of the trial.

In the document we recommend that there exists a DMC charter or standard operating procedures and that such a document be developed in advance of the instigation of the trial, if possible, and in advance certainly of the initiation of any interim analyses.

The document also discuses the schedule and format of meetings. The schedule and timing of meetings is largely a function of the structure of the trial itself, the interim analysis plans that are an integral part of the trial, but that needs to be planned in advance believe

obviously there are a lot of logistic and administrative issues having to do with that.

The frequency of the meetings, as we've heard earlier this morning, has a lot to do with the specifics of the trial--how rapidly the recruitment occurs, how rapidly the end points are observed, and that sort of thing. All of these have to be taken into account with regard to how frequently the meetings occur.

Also mentioned earlier this morning is the possibility of teleconferences. That sort of thing should really be a part of the discussion in developing a charter or an SOP. When do we meet face to face and when do we have teleconferences?

Also the question of what is a quorum for this DSMB is important. It's much more important when the size gets beyond the size of three because you can have DMC meetings scheduled and have the inability to get together the entire committee, so it really is important to discuss what in essence is a quorum.

And then this sort of charter or SOP needs to delineate the data access. Who has access to what data and how much of it? And is it blinded or unblinded? That ought to be delineated and spelled out at the beginning of the process, hopefully before the trial begins but certainly before the interim analysis begins.

And then some discussion of the meeting attendees, and that's also been brought up earlier this morning. I'll discuss that in a minute as we go through the structure of a DMC meeting.

There has to be some clear identification of how conflict of interest will be assessed. Some of the DMCs I serve on, there is a reassessment of conflict of interest on an annual basis and it's a very clear process. It's very helpful to have that clearly identified in this charter or SOP.

And then the method and timing of the distribution of reports. Obviously we're still in the stage where most reports are produced on paper and so they have to be physically delivered. So how the DMC reports are delivered, at what time they're delivered, are they delivered to the hotel the night before the meeting, is the DMC expected to receive the reports hand-delivered in their offices seven days prior to the meeting or by FedEx to their home doorstep? All of these things have to be considered.

There has been some discussion of the statistical methods already. All of this really does need particularly to be spelled out in advance of the trial. The statistical methods to be used may cover a broad variety of possible approaches--group sequential analyses, possibly Bayesian

methods, other methods. Certainly we talked about trials being living things. Statistical methodology is a living thing, as well, developing over time so the approach that is intended for this trial does need to be spelled out.

Also very important is the discussion of how the type 1 error rate is to be handled, how the type 1 error rate is to be allocated throughout the course of the trial. All of this needs to be very carefully spelled out in advance.

There also should be some consideration in advance of the conduct of the trial if and when a futility analysis should be considered, so that should be an issue that is at least discussed in advance.

And one of the things that DMCs are charged with is finding a balance between the risk and the benefit, so how this risk/benefit assessment is expected to be conducted. On occasion, DMCs see data that provide a certain amount of information with regard to the benefit but they don't necessarily have a solid handle on the measure of the risks, so their recommendations to the sponsor may be somewhat a function of which side of this equation they have more information on.

Again these are the types of issues that need to be addressed and considered in advance of the interim monitoring process.

Confidentiality we have already discussed to some extent but I think it's a general agreement--I hope it's a general agreement--that the interim comparative data are generally considered confidential, highly confidential, during the process of the trial conduct. The sponsors should establish existing procedures to ensure the confidentiality of the data. We've already heard examples where the possibility of knowledge of the interim data could affect the trial conduct and some examples of those are when there is an unstable situation, things are fluctuating and changing very rapidly. There may or may not be an emerging trend. It may be a solid trend that we see. We see this morning how long it's taken the economic community to agree that we're in a recession so it may take a while for emerging trends to be recognized.

Then we have the situation of interim reports. The knowledge of the interim report is not necessary for the investigators and/or the sponsors to do their job. Otherwise they wouldn't be in the process of conducting a randomized control trial and particularly a blinded randomized control trial. So we have this scenario where we have a data monitoring committee charged with monitoring the on-going trial.

The interim reports obviously have to be based on a prior established analytic plan, which is spelled out

usually in the protocol and possibly in greater detail in later documents. We've already touched on the discussion of the statisticians preparing the report and their level of independence from the sponsor.

I mentioned the issue of the timing and the distribution. The timing of when an interim analysis takes place should be a part of the plan, at least fleshed out in terms of how we intend to approach this issue, if not specifically nailing down the timing to the exact date for each of the interim analyses.

And then the comparative results usually are prepared in a printed report in a coded fashion, and by coded I mean blinded. The columns are labeled treatment A and treatment B or treatment 1 and treatment 2, and that sort of thing. Then in the process of the data monitoring committee meeting, the data monitoring committee has access to the unblinding of those codes. That is one additional level of protection.

I do remember a situation where a data monitoring committee member was en route to a data monitoring committee meeting and inadvertently left the monitoring committee report on the plane, so it really is useful to have these reports printed in a coded, blinded fashion for that reason, if for no other, but certainly there are many others.

Now with regard to the specifics of the meeting, there are separate parts of the report that are useful and used in the open and the closed sessions of the meeting and I'll go through the parts of the meeting that usually take place in a data monitoring committee meeting.

Here you see the meeting starts with an open session, followed by a closed session. There is potentially or optimally an executive session and lastly, a debriefing session. I'll go through each of these in some detail.

In the open session those attending the open session are possibly the steering committee, certainly the statistician who presents the interim reports for the DMC review. There may be some representative from the sponsor. There may be the individual, the principal investigator or the individual who serves as the study chair. There may in the open session be regulatory representatives attending.

In an open session only the aggregate data are presented--the total number of people who have enrolled in this trial to date, and so forth. There is an opportunity for communication of possible problems that the sponsor might be able to take some action about. For example, in an open session I have been involved in discussions of does this placebo taste like it's supposed to taste, and everyone in the room was given a placebo tablet to taste.

Those are the kinds of issues that can be discussed in an open session.

Discussions of implications of possible external research. We've heard mention of this issue and possibly this is going to come up more frequently. As research of this type is more globalized we'll hear about results from trials in Japan and need to address the issue of how do those results impact the trial that we're reviewing in front of us?

Then there is the opportunity to communicate without disclosing the comparative data. One can communicate that there are some enrollment problems, there's some problem with the laboratory, there's some problem with getting the data submitted centrally in a rapid fashion and that sort of thing. All of these types of issues can be communicated in an open session.

The kinds of topics that I've already mentioned--the accrual rate, the baseline characteristics, whether or not there's a problem with regard to compliance, whether there are problems with missing data, if the amount of missing data or the timing of how rapidly that missing data is retrieved, if at all possible, or if it's impossible to retrieve. That sort of thing can be discussed in an open session. The overall toxicity picture, if it doesn't provide information that unblinds the trial, and then the

site-specific issues--if there's a problem with one site or if, for example, in the VA system, and Bill can correct me if I'm wrong on this, they sometimes identify more clinical sites than they need so they have one or two back-up sites and if a site is not performing, then they bring in the next team.

Now to the closed session. In the closed session only the DMC members and the presenting statistician are recommended for attendance. The document discusses who should attend the closed session but it really should be a much, much more limited group of individuals than those in the open session, and we've already touched on this topic a little bit already this morning. And it is in this session that the comparative unblinded data are discussed and presented in detail and it is at this session that the recommendations, the formal recommendations to the sponsor are formulated among the DMC and a consensus is arrived at.

So that's the number of slides devoted to the open session, and the closed session don't necessarily reflect the relative amounts of time allocated to the open session and the closed session but they do delineate what gets covered in those two sessions.

Then there is the possibility of an executive session. As I mentioned, that box was a little off to the side because it doesn't necessarily occur at every meeting

of the data monitoring committee. There is or is not an executive session when the sponsor representatives have participated in the closed session and the DMC wants to meet and discuss only among themselves. There may be other issues that are appropriate for discussion in an executive session--topics dealing with study conduct, dealing with how the interim analyses are being conducted, dealing with the review process itself, dealing with the external study results, et cetera. This is again the session wherein only those members of the DMC are present and no one else.

Then at the end of the process there is a debriefing session where the DMC chair meets with either the representative of the steering committee or the representative of the sponsor or whoever the individual is who represents the sponsor in the context of delivering the recommendation and possibly orchestrating, taking some action on the recommendation.

There may be other issues dealing with the study conduct that are discussed in this debriefing session. There may be some clarification of the concerns that the DMC has and the specifics of the recommendation from the DMC to the sponsor to the organizing team of the trial are conveyed in this context. They're conveyed in this debriefing session verbally but again they're conveyed in a written form, as well.

The specifics of the DMC responsibilities. The organizational structure, the individual expertise represented within the DMC, the SOPs that we've already discussed, the analysis plan, the interim reporting, the meeting structure are all put into place to support the DMC in fulfilling its responsibilities and those responsibilities are listed here, the primary ones being to evaluate the accumulating data with regard to both safety and efficacy, to provide a recommendation whether or not the trial is to be terminated or to be continued as it was originally designed or possibly to be modified in some sense.

The other responsibilities of the DMC are to review and approve the protocol. Possibly this comes in in some DMCs that they receive the protocol before the trial is initiated and they review and approve the protocol. This doesn't necessarily occur in 100 percent of the cases.

They have some responsibility for assessing the trial conduct and we've discussed the differences between the IRB level of review and the DMC level of review so there are a lot of ways in which the DMC can review the trial conduct, but they are certainly not the only ones involved in this and they may in some sense, recommend additional analyses either to be conducted at the time, at the moment, or just prior to the next DMC meeting, or

possibly recommend analyses that the sponsor might want to undertake at the end of the trial.

The primary responsibilities--again, monitoring safety and effectiveness, to focus on the monitoring of trial conduct, to deal with any external information that might emerge. We've already talked briefly about involving DMCs in the process of early development, involving DMCs in monitoring phrase I trials. That sometimes is a responsibility of the DMC.

A major responsibility is to convey recommendations in a clear and useful fashion to the sponsors and the DMC is also responsible for meeting records--not only the terse, sometimes cryptic but hopefully usefully written but not conveying or unblinding the trial recommendations in writing. That's one of the meeting records but the other meeting records are transcripts or minutes of the DMC meeting, which are kept but usually are not widely available until the end of the process, until the trial is concluded.

Then there is the issue of who should have access to the treatment codes. Should the DMC review the comparative data? Some DMCs discuss this and choose to remain blinded until some later point in the interim analysis process when they choose to unblind themselves, but this is the kind of discussion that needs to go on at

least within the context of each DMC: who should have access to these treatment codes and when should the treatment codes be identified?

There are arguments in favor of remaining blinded, that the recommendations with regard to termination or continuation are seen in a different light when it's known that the DMC is in favor of blinding and remaining blinded. Other emerging concerns are seen in a different light when they're known to remain blinded.

Then there are arguments against blinding, that the DMC, if anyone in the process should be knowledgeable about what treatment A versus treatment B means, it is the DMC. So this is the kind of issue that really at the moment remains up in the air for how the individual DMCs deal with this, whether they remain blinded from the beginning or they unblind themselves once they begin discussion of treatment A versus treatment B. That's the kind of thing that needs to be discussed in the development of the charter, of the SOPs, and how each DMC chooses to operate within itself.

The DMC reporting, as I mentioned earlier, needs to be a report to the sponsor, a face-to-face debriefing, but then a short report to the sponsor after each meeting. The minutes, as I've already described, they go into a lot more detail as to how the recommendations were arrived at

and they are available only to the DMC during the conduct of the trial. Usually at the end of the trial those minutes and all the records involved in the process are made available to the sponsor and to the FDA at the completion of the trial.

So thank you very much.

DR. LEPAY: Mary, thank you very much.

We're going to adjourn for lunch now and we'll resume again at 1:30, again continuing this particular section of the document, and then into our second panel. Thank you.

[Whereupon, at 12:04 p.m., the meeting adjourned for lunch.]

A F T E R N O O N S E S S I O N

[1:32 p.m.]

DR. LEPAY: Okay, we're ready to resume for the afternoon to continue the discussion of the second group of sections of the guidance document. I'd like to open the afternoon session by introducing Dr. Jay Siegel, who's director of the Office of Therapeutics Research and Review in our Center for Biologics. Jay will be talking about a subject that I think we've hit on already on numerous occasions this morning but we'll certainly develop much more this afternoon and that is the independence of data monitoring committees.

INDEPENDENCE OF DMCs

DR. SIEGEL: Thank you, David.

Well, based on this morning's discussion I anticipate that this topic should lead to a lot of lively discussion and valuable input and I very much look forward to that.

So let me start the next half hour or so by outlining what's in the document and also by providing some case studies or examples that are, in part, informative about why the document says what it does.

A lot of people, of course, talk about independence of a data monitoring committee and very few

times is it well defined what one means by independence. When you write a document you sort of have to do that if you want people to understand the document.

So for the purpose of this document, at least, we start with a definition of what independence is and what we're addressing. No data monitoring committee is, in a true sense, fully independent by the sponsor. They're usually selected by the sponsor, paid by the sponsor, they make their recommendations through the sponsor, as some people have pointed out, but there are critical independence issues that are addressed in this guidance document.

So in Section 6 of the document at the very beginning on independence is this passage, which defines what we mean by independence. An independent data monitoring committee is a committee whose members are considered independent--good way to define it--of those sponsoring, organizing and conducting the trial. That is, they have no previous involvement in the design of the trial, are not involved in its conduct except through their role on the data monitoring committee, and have no financial or other important connections to the study sponsor or other trial organizers. And what we mean by important connections we have a little more detail on and that I'll come to in just a couple of slides.

So that's the working definition for this part of the document.

I would note that, as I said, we discuss both financial connections but we recognize that there are other types of connections that can compromise objectivity or create compromising situations, and I'll go into that in significantly more detail shortly.

The document then proceeds to discuss some of the typical relationships that a sponsor may establish in terms of their role on the DMC. At a time when they establish the DMC they'll define what their role is and that is a critical decision process with important implications.

There are two types of roles which are not consistent with the definition of independence, which is not to say that the document says that they're per se unacceptable; it just say that they're not independent, and it goes on to talk about the concerns or implications of that. Those are situations where the sponsor has a representative who is a voting member on the monitoring committee or where the sponsor has a representative as a nonvoting member on a monitoring committee but who is present at all sessions or, at the very least, at closed sessions, even if not executive sessions.

There are two other common conditions that are more consistent with the definition of independence where a

sponsor representative is present only in the open meeting and they may well see enrollment, compliance and event rate data but no study on specific data, or situations where the sponsor has no direct representation on the data monitoring committee.

The document proceeds to discuss three reasons why independence of the data monitoring committee is a desirable trait. I noted that Janet Wittes this morning, in pointing out that we were blurring some distinctions of important issues, summarized these issues much more succinctly than we managed in the document when she said we were blurring issues of confidentiality, credibility and conflicts of interest. And indeed there are different implications for each of those and certain other factors that contribute to the desirability of independence, so we've tried to take them somewhat apart and address them somewhat separately of each other.

The first reason given is that independence ensures the ability of a monitoring committee to make recommendations on behalf of the subjects and the trial, their two principal responsibilities, that are not unduly influenced by the interests of the sponsor. That particular issue is addressed in a passage in Section 4.1 of the document, not in Section 6, which deals with

independence per se, but in Section 1.4, which Mary alluded to briefly; that's the section on selecting a committee.

The second point, that complete blinding of the sponsor allows the sponsor to modify a trial or to take part in modifications of a trial without the introduction of bias. That's probably the issues that's the main focus of Section 6 and will be a substantial focus of the remainder of my presentation of Section 6.

And blinding also protects the sponsor from pressures toward premature disclosure. We've heard from CEOs of companies, for example, that if they learn the data and then attend shareholder meetings, get called by financial analysts, have to consider the lawyers telling them what they do or don't need to disclose to the Securities and Exchange Commission, that often they're put in rather compromising situations where there are pressures to do things that could endanger a trial.

Not explicitly on this list of reasons for independence but also addressed elsewhere in the document is the fact that keeping the DMC independent of investigators and sponsors decreases the likelihood that investigators, directly or through the sponsor, might become unblinded to the trial, which can impact recruitment practices, patient management practices, and so forth.

So in Section 4.1 is a passage on conflict of interest-type issues. It notes that data monitoring committee members should not have financial interests that could be substantially affected by the outcome of a trial, that they should not be investigators entering subjects into the trial. That reflects, as I just noted, not just conflicts of interest but also potential biasing impacts of unblinding.

They should not have strong views on the relative merits of the intervention and they should not have relationships with trial leaders that could be considered reasonable likely to affect their objectivity. This gets back to that issue in our definition of other important connections to the study sponsor.

We don't go into any detail on this issue. We recognize that the clinical trial community is a relatively small community, that members of the monitoring committee are, in fact, often people that may have important professional or other relationships with the people involved in managing the trial or conducting the trial. The critical issue, though, is to consider in these cases whether the nature of those relationships is such that they would be or would be viewed as being reasonably likely to affect objectivity.

Now there's a substantial value to a sponsor having certain types of involvement with a DMC, even an independent DMC, and that has already been discussed, I guess, in Mary's presentation regarding open sessions, and it's also discussed to some degree in Section 6.2 of the document.

These interaction can both facilitate the DMC's deliberations as well as facilitate drug development by the sponsor. And they may include sharing of information in both directions, and typically do, where the sponsor can inform a committee about what the sponsor's goals are, their plans for drug development, time lines, other trials, what indications they're seeking, how they feel about certain patient populations that are or are not in the study, dosing issues, and so forth, what resources they have committed to development of the product, what is and isn't feasible to do.

And conversely, by learning, the data monitoring committee can assist the sponsor in its role and the information in the open sessions can assist the sponsor in terms of discussion of issues with the trial regarding enrollment, compliance, event rates, and the like, that can be important determinants of cost, timetables, likelihood that the trial will successfully answer its questions, and so forth.

Section 6.3 of the document covers some of the risks that occur if a sponsor is exposed to interim comparative data, one of them being, as I alluded to before, the possible further unblinding of the trial so that investigators or participants in a trial, perhaps through a sponsor meeting with the steering committee and so forth, may learn directly or more indirectly about the data in the trial and that, of course, can affect various aspects of their role in dealing with the trial.

The other area which I've alluded to and will go into more detail on is, and also a number of examples shortly, is that the exposure to interim comparative data can significantly impact the ability of the sponsor and potentially others, as well, to manage a trial appropriately. And what we've seen over experience is that there are not infrequently, more commonly than anticipated by many, who would say you design a trial and you just stick with it to the end, there are not infrequently external factors that may suggest the need to change a trial. You learn something from other clinical studies of the same or related agents about what doses do, about what risks or adverse events are. You may have new financial resources or new financial constraints that may affect the way the trial can be conducted or should be conducted.

There can be internal factors to the trial, as well, problems, as I alluded to before, with compliance with the drug, with enrollment in the trial that may suggest a change in entry criteria or in the protocol that may be important for the success of the trial.

Knowledge of the interim data, when modifying the trials, may lead to unavoidable and uncorrectable biases. So if the sponsor and/or steering committee and other individuals involved in suggesting changes--changes to the analysis, changes to the entry criteria, changes to the protocol--are aware of results, unblinded results of the trial, they're likely aware of how that direct information as to whether changing that end point or entry criteria will increase or decrease the likelihood of success, that introduces biases to the trial.

Furthermore, these are not correctable biases in the sense that if you do multiple interim analyses you can apportion type 1 error to correct for that multiplicity to ensure that you don't have excessive type 1 error. When you biases that result from making decisions based on advanced knowledge, there is no statistical correction. You're just left with a trial result whose validity is called into question.

Section 6.4 is a section that has already received substantial discussion and I suspect will receive

substantially more and I would like to take this opportunity to urge all of you to read that section, for starters, as there were some comments that indicated that the document didn't cover areas which it does or that it says things which it doesn't.

So please read that section and please comment on that section. We know there's a great deal of interest. We know that it's a very common practice in all settings for statisticians as well as data coordinating centers that are unblinded to the trial to also be interacting with and preparing data for data monitoring committees and also be interacting in various ways with the sponsor of the trial.

That topic is addressed in this section. The section doesn't say don't do that or you can't do that but it does warn rather explicitly about some of the potential that has occurred in some cases to seriously impair the ability to manage the trial, to modify the trial, or to render a trial uninterpretable when certain types of relationships like that exist and we feel that it's very important that in deciding on the relationship and role of the statistician and coordinating center and the communication links, that these issues be taken into account.

So the sponsor statistician frequently is the one who sees and prepares the interim data, interim data

reports, and often, as well, presents them to the data monitoring committee. Experience has shown that separation of these statisticians from trial management may be difficult to effect or to demonstrate. It may be easier than we think but certainly in recent experience it hasn't always been accomplished to the extent one would hope.

So we find statisticians meeting with the trial team in the company; they're part of the project for that drug. We find these unblinded statisticians reviewing protocol and analysis amendments or sitting in those meetings even if not giving verbal communications, potentially giving informal or nonverbal communications and we tried in this section to explain what sorts of concerns arise from that--the notion that if a company or sponsor--it doesn't have to be a company; it could be a governmental institute--is considering a modification that impacts spending of millions of dollars and the statistician is there knowing potentially that the modification is futile, unnecessary, going to turn the trial into a failure, you know, and everybody knows that the statistician knows and he's just sitting there in the room not saying anything, that's a difficult situation and a difficult situation which really, I think, runs the risk of transformation of information, even nonverbally or verbally.

In other settings where maybe a corporate management is responsible for making those decisions there may be further pressures.

I think even where those pressures don't exist one of the concerns and one of the concerns we've raised is simply it's hard to participate in a decision knowing information and not letting that information contribute to the decision and it's hard to be present as a decision is being discussed or made and not be totally nonparticipatory. Those issues are addressed in Section 6.4.

One issue you used to hear discussed a lot at meetings and I guess still is sometimes on data monitoring committees and on interim analysis is the notion that was sometimes referred to as administrative looks, although I don't think we've used that term in this document. But the sponsor does frequently desire access to interim data for what are legitimate business purposes. They may want to know that they should upscale production, they need to plan another trial, they can get the drug to market perhaps a year earlier if they have an educated guess as to whether or not the trial is likely to be successful than if they don't.

However, there are some significant problems with these sorts of looks at the data. As I've just pointed

out, they may impair the ability to manage a trial. They may make the results uninterpretable due to bias. And although not mentioned in this section although discussed elsewhere, they may lead to further unblinding of the trial. So presumably if the sponsor sees the interim data and then starts building a new plant, that might well tip somebody off that there's a problem.

In addition to cautioning about reasons to consider not doing this in the first place, the document does provide some substantial guidance based on experience in terms of cautions that could be taken if a sponsor does choose to access interim data.

First, to consider discussing the issue with the FDA in advance. Think about the implications. Think about how to do it.

Second is that there should be a prospective stopping rule in a type 1 error allocation. We reject the notion that you can look at the data and have no chance of stopping the trial and therefore don't need to allocate any type 1 error. We believe that from an ethical perspective any time you look at the unblinded data you might see something that leads you to believe the trial should be stopped, that even if you assign a very low type 1 error if you think it's improbable, it's much better to do that prospectively than retrospectively.

We believe and advise strongly that the sponsor determine the minimal amount of information required. If what you really want to know is that the conditional probability of the success based on, say, your alternate hypothesis, is 60 percent, you don't need to see all the data from all the trial; you just need to know whether the conditional probability of success is over 60 percent or under 60 percent.

Having determined the minimal amount of data, we'd recommend that the trial formulate written questions so that they get exactly what they want and that there is a written record of exactly what was requested and what was given in terms of information, that those preferably be yes/no questions. "Is this number over 10 percent or under 10 percent?" Not "What is the number?"

That they receive only written communications from the DMC where possible, not meet with the DMC. We know that, of course, there's a lot more that can be communicated in person and that can certainly have its advantages but it also raises substantial concerns about the implications for the trial in what is a very dangerous situation when such meetings occur.

There should be standard operating procedures that identify who needs to know and access the information and that ensure that others do not have access to the

information. And the individuals with access should avoid any further role in trial management and should avoid taking actions that might allow others to infer what the results are.

The use of efficacy data from an on-going trial is discussed in Section 6.6. It's very uncommonly done. It's not uncommon to have safety reports that contribute to a labeling if it's an important part of the safety database and the trial has a long way to go to completion. Efficacy data would be very uncommonly done and it's generally ill advised because it might endanger the trial. However, there are exceptional circumstances that may arise, that have arisen on rare occasions, and we advise that before accessing and using data in a regulatory submission sponsors should talk to the FDA, as well as the data monitoring committee, to consider the implications of using those data, and also to consider approaches, such as what data should be looked at, who should look at them. Can they go straight from the monitoring committee to the FDA without going through the sponsor? That's been done in some cases to help preserve the integrity of the trial, and so forth. Those issues merit discussion before decisions are made.

I'm going to conclude this talk with a few brief case examples that exemplify some of the problems that have

arisen, some of the issues that this guidance is trying to alert to. I have three examples--I have four examples. I have three examples that specifically have to do with involvement on the monitoring committee and access to interim data. Of the three, one is at the NIH, two are industry examples. Two involve data coordinating centers and two involve sponsor statisticians, so we have some good food for that discussion and debate.

I'm sure a number of you are familiar with the studies about 10 years ago of HA-1A, an antibody to lipopolysaccharide for treatment of patients with sepsis. At a particular point in time two-thirds of the data had been reviewed at an interim analysis. Of note for this difference, the sponsoring company's vice president for research and development attended the closed session of the monitoring committee and viewed the interim data. In addition, the statistical coordinating center, which was a private organization contracted to by the company, prepared the data monitoring committee report and the president of this statistical coordinating center also chaired the data monitoring committee.

Subsequent to this interim analysis, the sponsor submitted a revised analytic plan to the Food and Drug Administration. They told us that they had not seen any of the data at the time. The plan modified the primary

analysis, changing from 28-day to 14-day analysis, modified subgroups. There were different groups of gram negative infection and sepsis and gram negative bacteremia groups that modified which groups were important to the analysis, changed to a rank analysis from a point in time analysis, a landmark analysis of survival, and made many other clarifications because the original analytic plan was rather vague on a number of issues, made a lot of useful clarifications but also some significant changes.

These changes were made by people who had seen all the analyses, both those that were defined by the original protocol and defined by the new protocol. They weren't fully made by those people, in fact, but they were reviewed. The new plan had been signed off by this vice president and by the statistical center, both of whom had seen unblinded data but assured us that they didn't allow that to bias or influence their decisions on the acceptability of the changes.

The outcome of this situation was that these changes, once we learned the conditions under which they were made, raised in our minds and ultimately in the public mind considerable questions about the validity of the data. We attempted to revert to original analytic plan, although it was somewhat ambiguous in a number of areas. Other issues arose from the fact that the sponsor had

misrepresented the situation and that led to some significant implications that I won't digress into.

There may be some misunderstanding. The product was not approved but it was not not approved largely for these reasons. It was not approved because their trial was not a successful trial, although it had been published in the New England Journal as having a mortality P value of 0.012. By our assessment of the best prospective analysis the P value was 0.6. We requested a confirmatory trial and that was done and it was stopped for the safety stopping rule with a trend toward excess deaths on treatment.

Actually I'll come back to that trial in example number 4 if time permits.

The second example is an example of the development of PPA, tissue plasminogen actovase, altoplase, whatever. The trial was the Neurologic Institute-sponsored, a phase II placebo-controlled trial. The primary end point of this trial was neurologic function as assessed at 24 hours. The secondary end point of their trial was the functional status of the patient, their level of disability, residual disability, at 90 days. It's the secondary end point that's the one that the FDA recognizes as an appropriate type of end point for approval of a drug, the primary end point, a useful end point potentially for

drug development. That's, of course, up to the sponsor to choose.

Now an interim analysis had been conducted with about three-quarters of the data in and at some point in time subsequent to that the steering committee of their trial, which was largely blinded to this interim analysis, proposed switching the end points and increasing the sample size. They felt that it could be very difficult to do a confirmatory trial in this setting. If the trial was successful and if the secondary end point was successful, since the drug was already on the market for treatment of patients with myocardial infarction, that physicians could just use it and if they could just use it, they may not be willing to enroll patients for their successful trial so they should make this more definitive by making the primary end point, the clinical one, increasing the sample to power it.

The problem with that proposal, which was a logical one on the face of it, was that the statistician, who was also the study coordinator and worked at the study coordinating center, was unblinded and this statistician had joined the steering committee when the proposal was formulated. So the statistician met together with the committee, did not share the unblinded information but was part of the discussions that led to this proposal. Then

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the statistician came to the FDA and presented this proposal to switch the end points, together with some other members of the steering committee and to change the size of the trial.

In this particular case the agency felt that there was just no way to know the amount of bias that could have come into this by the fact that that study coordinator knew both what was going on with the primary end point and the secondary end point, knew that this was either a very good idea or a very bad idea in terms of the ultimate desire of the institute in proving the drug effective or not, and that despite the best intents of the institute and the study coordinator, that that could introduce uncorrectable bias and shouldn't be done.

We said they should simply complete this trial and start another trial with alternative end points, with switching the end points. They did that. They worded it and published it as part A and part B of the same trial but they were separately analyzed, as we proposed and suggested. And in fact, it turned out that both trials gave essentially identical results, which was a very strong positive finding on both sets of end points. It turned out that the interim data that had been viewed by the study coordinator showed actually a more powerful finding on the secondary end point of functional status at 90 days than on

neurological function at 24 hours, suggesting that the switch would have been one that would have been good for success and wouldn't even have required the extra people for powering.

And again, knowing that the study coordinator knew that information and participated in those discussions, we felt essentially rendered it impossible to make those changes without the potential of endangering the trial.

It's probably a good idea in that particular case that there were, in essence, two trials because thrombolytics can cause intracranial hemorrhage. There were other studies that were done previously and subsequently at different doses with different drugs or in different patient populations, not as rapidly treated perhaps, which haven't achieved the same level of success and I think there's still a significant question in the field as to exactly when and in whom this treatment is more useful than harmful, but the fact that there were two successful studies was, I think, a very important part in terms of the development of that treatment.

My third example, which I'll try to go through quickly, of this sort of modification of a trial was one in which there was interim data from most of a phase III trial--I don't have the exact numbers with me--that had

been prepared by the sponsor's statistician for review by the data monitoring committee.

Subsequently, the sponsor decided the trial had been underpowered. Basically they said well, we always knew that our estimated treatment effect was too high but it was based on how much money we had available from management to do the trial and now they gave us more money and we want to be able to power to do a larger trial.

Well, this happens and you know, larger trials tend to be better than smaller trials. Of course, the problem is if you've looked at the data at the end of a trial and you say well, our P value just missed so we're going to extend the trial a little longer to turn it into a success, that would have some rather problematic effects on type 1 error and we didn't know, of course, the extent to which that may have happened since, at the very least, the statistician who was part of the sponsor's organization planning the trial was, in fact, aware of the interim data. As this notes, the sponsor's statistician sat on the trial planning team and attended internal meetings to discuss and decide upon the extension.

In this particular case the company went to the lengths of getting sworn affidavits that no, the sponsor never talked to anybody. The affidavit didn't mention whether he smiled at somebody or nodded when they proposed

these changes. It clearly was millions of dollars additional being invested into a drug that was going to mean hundreds of millions or billions of dollars to the company so at least the concerns certainly were there that somebody might have wanted to know what the statistician knew and that the statistician knew information that may have influenced his participation and role in the trial.

We did allow the increase in the size of the trial, since we thought that it would provide useful information. However, in this particular case we expressed our reservations in terms of how we would interpret the data under certain circumstances.

That's the end of my talk but I'm going to take just a minute to present one more example that really fits in better with the next session about interactions with the FDA, which is being presented by Bob Temple, but he suggested that it would probably be better for flow if I mention it here. This one is really about the FDA ourselves knowing interim information about trials.

The CHESS trial is the trial that was done to confirm whether HA-1A really worked in sepsis. It was initially named confirming HA-1A efficacy in septic shock but when it failed they changed the C from confirming to the name of the company actually, which I don't mention here, or something like that. I thought that was kind of

cute. They thought it was unethical to do the trial because they were convinced that it had to work.

In any case, the interim analysis showed a strong trend toward harm. It was .07, one-tailed, I think, toward harm. That met a stopping rule. It also met a futility stopping rule and the trial was terminated the next day on the 17th. This is in '93.

At the same time there was a trial in a related but different condition, meningococcemia, a type of sepsis but a different pathophysiology and affecting very young children, but because of the excess deaths in this trial they suspended enrollment. And then they asked the FDA the next day, on Monday, they came to the FDA--we had already read the news--and said all of this has gone on and we'd like you to look at the data from the meningococcemia trial to determine if we can't restart that trial because of there were concerns that the drug might be harmful; on the other hand, it might be very different in their trial and helpful and the company wasn't sure the best way to proceed.

The FDA in this case, as we do in many cases or in a number of cases, looked at who was on the DMC and how well constituted it was because we have an important obligation to protect safety of patients in this trial, as well. On the other hand, we have a desire not to unblind

ourselves, where possible, because of our potential role in considering changes to a trial and the way in which that can be biased by knowledge of the data.

In this case we had an excellent data monitoring committee, a lot of experts in the field. I remember Janet Wittes was on this particular committee and others. We felt that this data monitoring committee, if they saw the data from both the CHESS trial and the interim data from the meningoccemia trial, was well constituted to determine the appropriate fate of this trial without unblinding the FDA and we suggested to the sponsor they have the committee meet immediately with that information.

The monitoring committee recommended continuation and interestingly, about two years later in that trial the sponsor did propose some significant changes to their trial and we were pleased to still be blinded to the data outcome as we considered that proposal.

And with that, I'll thank you for your attention.

DR. LEPAY: Jay, thank you very much.

I'd like to invite the members of the second panel to join us here, and Mary, as well, and perhaps I can also get some assistance from the audiovisual people, since we won't be needing the slides until after the break.

I'd like to go down the line of our distinguished panelists for the second panel. Dr. Thomas Fleming, who's

chairman of the Department of Biostatistics and professor of statistics at the University of Washington Seattle. Norman Fost with the Department of Pediatrics and the program in medical ethics at University of Wisconsin in Madison. Larry Friedman, special assistant to the director of the National Heart, Lung and Blood Institute at the NIH. Ira Shoulson, professor of neurology, medicine and pharmacology and Louis Lazania professor of experimental therapeutics at the University of Rochester. And Steven Snapinn, senior director of scientific staff at Merck Research Laboratories.

I'd like to follow the format that we tried this morning and ask if each of the panelists could perhaps deliver a few remarks in response to their own experiences and what they've heard today and hopefully this will help us, as well, develop comments that will be useful in our review of this particular guidance document.

So with that I'll start with Dr. Fleming.

DR. FLEMING: Certainly this topic of data monitoring committees is rich, complex and controversial. And while a 20- to 25-page guidance document can't be comprehensive, I've been very impressed that this has been extraordinarily well done in really capturing in many areas the essence of many of the key issues.

The sections that we're considering here, one of the sections is Section 6 on independence. A quick comment. I'm very pleased that the document brings out the conflicts of interest here that we need to be aware of and need to take account of are not only financial but also professional or scientific.

I'll be focussing probably more in the few comments that I can make on Section 4 and as it relates to this in Section 6 on issues of confidentiality and let me just quickly touch on what I see as some key issues, maybe to expand a bit on what's in the guidance document.

First, in Section 6.4, as Jay Siegel had called our attention to, there's discussion about multiple roles of statisticians and you might characterize those in an oversimplification in two key domains, one being the role of the protocol or steering committee statistician being involved in the overall design of the trial and the role of the statistician who I might call the liaison between the data monitoring committee and the database.

And very quickly, I think there is a lot of wisdom in what's been discussed to consider the advantages of having those be different statisticians in that certainly the liaison has to be unblinded to the data, whereas the statistician who's interacting with the protocol team needs to have those interactions not only

during the design of the trial but during the conduct of the trial. Jay had raised some issues, for example, maybe there's more money available that would allow the study to be made much larger in size. Or maybe there are external data that come to light that might lead to the need to change end points or to change key aspects of the analysis and the statistician needs to be integrated into those discussions and, as a result, would need to be blinded. So I think it is something to consider as an advantage in having different people serving in those two roles.

Another issue in Section 4.3, an issue is brought to light that is something that I know has been on the minds of many of us who've been on monitoring committees. I did an informal survey of a number of statistical colleagues who'd been on monitoring committees and I asked them, what's your most frustrating or controversial issue? And it was surprising to me how often people mentioned as their first frustration proposals that the monitoring committee itself be blinded.

I think the fundamental issue that's concerned us is that our first and foremost role in monitoring trials is safeguarding the interests of study participants and to do so in a way that the data monitoring committee is uniquely positioned to do, it's critically important for that committee to have full insight. And I was pleased that in

Section 4.3 the document says the DMC should generally have access to actual treatment assignments for every study group.

Another issue that Jay and Mary Foulkes got into in Sections 4 and 6 relates to sponsor access to interim data for planning purposes. It was in Section 6.5. I guess I would in general argue that one should be extremely cautious about what you would be providing.

Now a related point comes up in Section 4.3, where there's discussion about the content of the open report and I would argue that much of what is there I would argue is certainly on target. The open report should be presenting data, aggregate data that gives a good insight about how the study is progressing and study conduct, issues that relate to overall recruitment, overall retention, overall adherence.

What's controversial, though, is should aggregate data on efficacy and outcomes or safety outcomes be presented in an aggregate manner? And I would argue there that can lead to great concerns. You may have an advanced cancer trial where you know that there's a 15 percent--you anticipate a 15 percent natural history survival at two years. If aggregate data show 25 percent or 10 percent, that could give clues about whether the intervention is working or not working respectively.

Or you may have a behavioral intervention looking at reducing transmission risk of HIV. If you look at the secondary data in the aggregate on behavioral effects and you see major behavioral effects, that may be interpreted as clear indication of efficacy or maybe even the need to change the primary end point. These are issues that I think have to be very carefully dealt with when one is considering what information should be presented in aggregate.

On the other hand, you may have an IL2 trial where you're looking at preventing HIV transmission and it's well known that IL2 is going to change CD4, so showing aggregate data on CD4 in that setting is simply getting at whether there's proper adherence. So it's an issue that needs to be thought through on a case by case basis.

Information in the open report is what I would consider as public information that could be widely disseminated. There is need in some cases for information on a more limited basis. A medical monitor may be needing to present information on a regular basis to regulatory authorities about emerging problems. That person must have access to the emerging safety concerns that are SAEs in an aggregate sense, to carry out their responsibility.

Or you may need to adjust sample sizes based on event rates. That information could be provided. I argue

it should be provided on a need-to-know basis. It should be provided only to those people who need to have access to that data to carry out those responsibilities.

Maybe just a couple of other really quick points. Mary talked about the chair this morning and I think one of the concepts that comes to mind there is the concept of consensus development versus voting. She had mentioned that one of the characteristics of the chair is that it should be a person who's a consensus-builder. I think that's an extremely important point.

I've often had it said we have to have an odd number of people on the DMC so that when we vote it won't come out tied. I object generally strongly to votes on DMCs. I believe that the DMC's responsibility should include discussing issues at a length and in a depth to arrive at consensus about what ought to be done. And I agree with Mary that as a result, the chair needs to be somebody particularly skilled at developing consensus.

Finally, as has been stated, there needs to be minutes of open and closed sessions. The sponsor's responsibility should be to ensure that those minutes are obtained. The FDA, in turn, I believe, should routinely request those minutes after the study has been completed.

DR. LEPAY: Thank you.

Dr. Fost?

DR. FOST: Thank you. I just can't resist commenting that Tom's comment about closed votes reminds me of the patient who got a telegram, "Union Local 221 wishes you a speedy recovery by a vote of 15 to 14."

I want to make four points. First, I was very pleased that the draft document has very strong positions and clear positions on the nondata analysis functions of the so-called data monitoring committee. That is, it says in a couple of places that these committees should review the consent form, that they should review the design of the study, they should take account of external information that may arise in the course of the study, all of which I agree with. None of those are data monitoring functions and it's important; it leads to two things.

First, it's important that it be in this guidance because in at least three DMCs that I've been part of, rather acrimonious fights erupted at the beginning about my raising these kinds of issues, charges being made that this is a data monitoring committee; those are IRB functions or steering committee functions; it's not for the DMC to do.

If it's important, as obviously the writers think it is, I think it would be helpful to put the reasons in there. It's just sort of stated and a justification is not provided for. The justifications are the independence of this group--it's supposed to form some independent

assessment of the propriety of the study--and the personal integrity of the DMC members. I or a statistician can't be participating in data monitoring for a study that we think is not protecting subjects because the consent is flawed or because the design is flawed or because there's outside information.

One more conclusion follows from that and that's the name of these groups. And with all respect to Susan's very good slide about the thousand different ways you could name these things, I think it doesn't make sense to call it a data monitoring committee. In fact, it undermines these nondata aspects. So I would much prefer that they be called independent monitoring committees or just monitoring committees so it makes it quite clear that the function of the group is something other than or in addition to just data monitoring.

Point number two with regard to the consent process, as an IRB chair I can report that almost never do consent forms these days tell the subjects about these data monitoring committees and particularly the part that the subject might be interested in knowing about, that the study may lose its equipoise well into the study while recruitment is still going on and while patients or subjects are still in it. That is that there may be in the course of the study good evidence that A is better than B,

but the study's going to continue because maybe A is more toxic than B. A recent anti-platelet trial showed efficacy early on but it looked like there was a lot of bleeding going on early on and how these things balanced out required some more time and some more data.

Now right now there are very few patients who know about this and maybe fewer who care about it but litigation is rising rapidly in this field--it's been relatively uncommon--and somebody is sure going to bring a suit or some critic is going to say this trial continued when it was no longer in equipoise; there should have been an agreement or a contract with the patient to do that. I think it's a boilerplate kind of paragraph that can be constructed and we're well on our way to 30-page consent forms but I don't know any way around it if we're going to include meaningful information.

So I would suggest that the existence of data monitoring committees and what they do in terms that would be meaningful to a patient should be in the consent form.

Third, having said that these nondata functioning activities are important, I want to say something against these activities or at least one of the problems with them that one needs to look out for.

First with regard to design, I don't know how you can not review the design when you join one of these

committees. If you think it's very faulty obviously you can't ethically participate. But I've been on at least three data monitoring committees in which the investigator became enraged when the data monitoring committee started making comments about change in design. You know, this had been under discussion for years, serious, intense meetings for the better part of a year, and now for somebody else to come in with a different view, maybe a legitimate view, but to say "Do it our way, not your way" was quite outrageous.

So when the committee gets involved in all this is very problematic. You can't be part of the planning of the study but if it comes in too late after the study has started and thinks the design is so faulty that they can't ethically participate in it, it can lead to very acrimonious discussions.

I don't know what the solution to that is but I think it's a hazard of getting involved in design. I think the answer is that the committee has to have a high threshold for going to war over it. That is, they should not demand some change in design unless it's something that's really very fundamentally wrong, not just "I think it would be better if you did it this way or the other way."

Second, the same kind of cautions arise with regard to the consent process. The risk here is that the

data monitoring committee takes over the position of the IRB or more commonly, competes with the IRB; that is, sees the consent form at the outset of the trial and says oh, this is faulty in some fundamental way and says it needs to be changed. So the steering committee is then obliged to send a note to all the IRBs in a multi-center trial requiring them to change the consent form but the local IRB may not agree with this change, so the investigator is caught in the middle.

And as an investigator myself and an IRB chair and a member of DMCs, I can say it's very frustrating for investigators, IRBs and DMC members to get buffeted about in this sort of endless loop of who has the final say over the consent form.

So again the answer to this I think has to be that the threshold has to be pretty high but having said that, I've been part of a DMB where halfway through a study involving 10,000 people, when new data came in from the outside involving risk of the study drug, we insisted that a revised consent form, that is, reconsent, go out to almost 10,000 patients. This was not appealing to the study directors but we thought it was sufficiently important because it was a major risk and we thought people should participate in it.

On the other hand, I've been part of a DSMB in which a consumer advocate who had had no prior IRB experience insisted on minute changes in the style and wording of the consent form and I think it was important for the DMC, while being sympathetic to a colleague, not to participate in that sort of micromanagement of the consent form because of this endless loop and the very long time that it can take.

With regard to these issues about the hazards of DMCs competing with IRBs, I mentioned to Susan during the break John Crowley, a statistician and former colleague at the Fred Hutchinson Center, has written on this, problems with DMCs replacing IRBs and oversight committees, steering committees, and particularly studies with cooperative oncology groups, and so on, where there's been quite a lot of vetting and good statistical consultation ahead of time, to have the DMC come in and start now micromanaging can be quite problematic. So there is a contrary view out there.

Last and a minor point just to repeat what Dave DeMets said the discussion this morning, something needs to be said in this document about local studies that can't afford full DMCs as to what a reasonable substitute would be. I think we've heard from several people and I concur heartily that an IRB can't be a monitoring committee; it's just way beyond its capacity. But something needs to fill

in there and maybe it's just saying something like hiring and independent statistician or a clinician or the two of them and having them review the data on an interim basis. So something less than the full detailed elements of the guidance but something that would be better than nothing. Thank you.

DR. LEPAY: Thank you.

Dr. Friedman?

DR. FRIEDMAN: Thank you. Obviously I'm going to be speaking from an NIH perspective so take that into account.

I thought the document as a whole was outstanding and brought up a number of issues which people have talked about for a long time but it's nice to see in a document that is going to be widely distributed. Having said that, I have a couple of points I'd like to make.

First, I think we have to remember why we do clinical trials and what our objective is in doing those studies. It's clearly to gain important medical knowledge, and certainly from the NIH it's public health-important knowledge. And simply conducting a clinical trial is just part of the overall way we go about getting that important knowledge.

Taking it one step further, a data monitoring committee is one tool to be used in making sure that we

have high quality clinical trials. Obviously it's a very important tool but it's just one aspect of study design, participant safety, and indeed monitoring because I would hope that others are doing monitoring on an on-going basis, as well. Clearly a data monitoring committee only meets occasionally and only sees the data in tabular form when other things will be going on on-line and people have to be able to react.

So that brings me to the point of independence. Yes, independence is important and I have argued for many years that a data monitoring committee has to be independent in the sense of not having a vested interest in the outcome. But to the extent that we concentrate on independence and forget about why we're doing the trial in the first place is a mistake and I think we have to recognize that independence is not the end of what we're--is not our goal. Independence, to the extent it's important, is another tool in making sure that all data monitoring is conducted appropriately.

To the extent that--and Joe Constantino brought this up this morning--to the extent that we concentrate so much on independence and forget the other aspects, which may be more important in given circumstances, I think we're doing a disservice to both the study and most importantly, to the participants in that study.

This comes up in whether or not we want a truly independent statistician to present the data who may not understand the protocol as well as someone who lives with it on a day-to-day basis, who may not know all the nuances of what's going on and may not have gotten all of the reports on a day-to-day basis.

So these are trade-offs that I think need to be considered. I'm not arguing necessarily against it but I think it's something that needs to be considered and it's not a necessary this-or-that.

Similarly, and again speaking from NIH, attendance by sponsors at meetings. I'm not talking about being members but attendance. Obviously it's important for NIH to know what's going on, to hear what's going on, because we have a broad mandate from the public to produce high quality research for public health purposes. And yes, of course, we want the best possible advice from "independent committees" but to the extent that that best possible advice is not communicated in a way that is optimal for our broad purposes is not ideal and I think we strongly need to think about why and when it's appropriate for sponsor--in my case government but potentially others--ought to be available and ought to hear the kinds of discussions that are going on so that the real objective, conducting the best quality study, is accomplished.

I did hear the comments by Susan and others how these are suggestions, guidelines, that it's not an attempt to make sure everything is the same, but I think there's a tone here that conveys a certain way and I think the document would be better if it were perhaps more open on some alternative approaches. Thank you.

DR. LEPAY: Thank you.

Dr. Shoulson?

DR. SHOULSON: I'll try to make my comments brief because it looks like you're running out of time.

Just a few things. I wanted to congratulate the agency for developing this document but also mindful of the fact that the document was really developed on the basis of collective experience in the past few decades, largely based on anecdotal shared experience, not so much in terms of a database that we can go to. And I think one thing just to keep in mind is that moving forward, we need to develop a database that we could tap into to really look at the experience of DMCs and hopefully this will be more of a prospective experience and a more systematic type of database, just as a general comment.

The other general comment about the document is obviously the audience of the document are sponsors, either sponsor's companies or sponsor's steering committees or CROs, and that's appropriate but I just point out that

there's an important group here, namely, the investigators in the trial and the IRBs which they are accountable for--and obviously in the long run they're accountable to the research participants and their patients--that needs to be addressed. I won't repeat many of the remarks made by Dr. Fost--I guess we share as investigators a lot of these issues--but I think it's important at the same time either in this document or in a subsequent version that's perhaps broader is to clarify the roles of the IRBs and the DMCs in regard to the monitoring of trials.

Obviously one difference is the IRBs are responsible for the up-front judgments in terms of benefits and risks, although they do have an on-going responsibility, and the DMCs, of course, have to look at accumulating data in the course of a trial.

I think one important part of a DMC is in its constitution that at least in terms of my experience, that the members should at least appreciate or share the equipoise that has been developed by the investigators and sponsors in the trial. If they cannot share that genuine uncertainty or appreciate the genuine uncertainty about the merits of the relative treatment arms then that would be a good time to decide not to participate.

There is, I think, an important role for sponsors and particularly companies that they sometimes delegate or

relegate to DMCs too many things that perhaps they're responsible for. For example, the stopping guidance, stopping rules as some would speak of them, I think really the first draft of this should come from the sponsor to the DMC and then perhaps get comments back on that until that's really developed. So I think that's an important responsibility of the sponsor.

Just a few other points. Training, I think, is a critical issue. I think we underestimate how we have insufficient expertise of clinical investigators, biostatisticians, bioethicists, that people really need it. And I think that we need to approach this in a more systematic fashion and I think that we need to think perhaps outside of this particular box about curriculum standards, credentialing and the type of database needed to train people on DMCs. And I know that just reading this document and hearing the discussion, this has been enlightening for me in terms of our own commitment to training of individuals involved in experimental therapeutics.

One point. I only counted once in the document that the word "medical monitor" was raised and this is an important person from the point of view of investigators and sponsors and I think that should be delineated a little

bit further in terms of that position in which the medical monitor sits--quasi-independent type of role in the study.

Finally, I just want to mention the importance of dissemination of information to the public. It was mentioned by Dr. Fost about IRBs. In our multi-center trials we have several IRBs who will not even review a trial unless submitted to them the composition of the DMC, the stopping guidelines of the DMC for that trial. And oftentimes, of course, this is not developed at the same time that the initial model consent form is. I think IRBs are doing this one, because of their commitment to ensure the safety and welfare of the research subjects but also they want to clarify what their role is and what the DMC's.

So I think this blurring of roles and delineation of roles is a very important issue that really needs to be addressed.

And the final thing I'll say about dissemination of information is that we need to educate the public in general, not just the public participating in the clinical trials, but the public in general about monitoring accumulating data and possibly performance in a trial. I think it's a very challenging thing to do but I think it behooves us and I think at the end of the day the public will be more competent about the value of clinical trials as a result of that. Thanks.

DR. LEPAY: Thank you.

Dr. Snapinn?

DR. SNAPINN: First, as a way of background, as a statistician in the pharmaceutical industry I've had the opportunity to play the role of an unblinded statistician reporting to DSMBs on a few occasions. Also I cowrote the SOPs that my company uses for interactions with for forming and for DMCs in general.

In reading the draft guidance I was very happy to see that with one or two notable exceptions the guidance is extremely consistent with our own SOPs but one of the exceptions, as you might have guessed, has to do with whether or not an industry statistician should be unblinded in reporting the results to the independent DMC.

Now the distinction between the two documents is not all that great. First, I think we all agree that the unblinded statistician in the sponsor should not participate in any discussions regarding the protocol, protocol modifications; those would be totally out of bounds. And this person should be isolated to the extent possible from the project in general and only doing the interim analyses and, in a sense, is an independent person working for the DMC for the purpose of that one study.

Now I suspect that we're going to have a serious discussion about this issue over the next half hour or so

but let me just start it off with maybe a less serious comment. It's possible that one of the reasons for the disagreement and one of the reasons why I and maybe some others in industry prefer to keep the role within the industry is that it's so much fun to do these analyses. Maybe fun is not the exact right word but it's extremely exciting and rewarding to be working on these trials, to watch the results emerge as the trial's progressing and usually it's an important and exciting medical research that you're involved with and you get to interact with the DMC, which, of course, is comprised of some of the world experts in the field. So if this role is taken away from the industry, the life of a pharmaceutical statistician becomes a lot less interesting.

Just a couple of other brief comments. First, I'm actually not very comfortable with some of the things in the document about the nondata functions of the DMC. Let me just bring up one example which maybe crystallizes my concern here. This is a trial, an experience I've had earlier this year where the trial was on-going, a placebo-controlled trial in patients with type 2 diabetes and while our trial was on-going some other results were published, other placebo-controlled trials with drugs in a similar class, with very positive results. So there was a question as to whether it was ethically acceptable for our placebo-

controlled trial to continue on the basis of this external information.

In the case of this study our fully blinded steering committee ultimately decided the trial had to stop; it was not ethical to continue it, which I was very happy with. My greatest concern was that the DMC would make a similar recommendation because if they had, I have no idea what the impact on type 1 error would have been. Would we be required to compare the observed P value with the interim monitoring P value, which, of course, is quite small--in fact, I think it was .001 at the time the trial would have stopped--or would it have been appropriate to ignore the interim monitoring guidelines and use the final adjusted P value of .045, say, to determine statistical significance in that trial?

If you would agree that .045 were acceptable then isn't there the opportunity for the DMC to consciously or subconsciously say well, the trial is leaning in the right direction, .02, .03, therefore I think we can appeal to the ethics of the situation and stop early? I mean isn't there the opportunity for that kind of a problem in this case of external data and maybe in some other cases of nondata functions of the DMC? So that has me somewhat concerned.

And just two other quick issues that I'll mention without giving an opinion on. One, I think we'd agree that

DMCs should have access to the database when questions arise during the course of the trial, that they should be able to request additional analyses. And I think we would agree that anything within reason is acceptable. But are there any boundaries? That's the question I think we could have some discussion on. Does the DSMB have carte blanche to request any amount of resources from the sponsor or from the coordinating center or is there some kind of a limit there?

And another question, I think the document mentions that the DMC's responsibility is to protect patient safety, patients in the trial and patients yet to be randomized. Question: does that extend to future patients and does the DMC have any responsibility to protect potential future patients, not necessarily just those who would be part of the clinical trial?

DR. LEPAY: Thank you.

At this time I think I'd like to open the discussion up to the audience and we can continue to pursue some of these topics with the panel in the course of this discussion. Again if people could step up to the microphone, we're recording this so please identify yourself.

OPEN PUBLIC DISCUSSION

MS. EMBLAD: I'm Ann Emblad from the Emis Corporation.

I wanted to make a remark about the definition of the independence of a DMC. With respect to the definition that says a sponsor should not have access to event data by treatment, I think that applies pretty well to efficacy data but I'm not sure it always should extend to safety data.

There are plenty of examples where these two things are intertwined. There are also examples where they aren't. One dear to my heart is eye disease, where a primary outcome would be vision, where a safety outcome may be mortality and I would contend that the sponsor has the ultimate responsibility for the patient's safety. Even whether they delegate this to a CRO or to a DMC, if something goes wrong, the buck is going to stop with that sponsor.

So because these are guidelines, they will become quoted and people will point to this definition of independence as the gold standard. I think there needs to be some softening of the language to consider, in cases where appropriate, that a sponsor may need and should have access to safety outcome by treatment, not just in aggregate. Thank.

DR. LEPAY: Any comment from the panel?

DR. FLEMING: Certainly in monitoring trials the sponsor, the regulatory authorities, the investigators, caregivers, patients are all very concerned about the best interest of patients both on the trial, as well as future patients and those concerns are more globally reflected by what I would call benefit-to-risk, which certainly is made up of both the relative efficacy profile and the relative safety profile.

There have been extensive discussions within this briefing document draft, as well as elsewhere, that broad access to such emerging data on benefit-to-risk can be very detrimental to overall integrity and credibility of the trial and providing access to one domain of that, i.e., the risk component, is certainly providing important insights about overall benefit-to-risk.

You also mentioned mortality. Well, mortality could be an integral part of the efficacy end point, as well. So when you have access to relative safety data there are certainly major concerns about whether that could lead to all of the issues of concern that have been articulated in the briefing document draft.

DR. SHOULSON: Just one brief comment. I actually think the ultimate responsibility for the welfare of research participants is that of the investigator. The contract is actually made at that level and that is the one

that has the enduring responsibility. The buck may start and stop with the sponsor but I think that--and, as I said, this document is focussed on the sponsor but I think we really have to be mindful of the agreement made between the investigator and the research participant in the oversight of the IRB.

MR. BLUMENSTEIN: I'd like to raise two issues.

DR. LEPAY: Please identify yourself.

MR. BLUMENSTEIN: I'm Brent Blumenstein. I'm a group statistician for the American College of Surgeons Oncology Group.

I'd like to raise two issues somewhat related. The first has to do with the confidentially agreement that the data safety monitoring committee has with the sponsor in light of the potential for the sponsor to act in opposition to the recommendations of the data and safety monitoring committee. And the second is related to when the role of the data monitoring committee ends. And those two things are related because there are representation of results issues that could extend beyond the time when the results of the trial become known and are published in public forums or in peer-reviewed literature.

The ultimate judge of the data in an industry-sponsored trial, of course, is the FDA and the FDA gets a chance to look and scrutinize the data but in the meanwhile

there can be a lot of things that are done to represent the results of the data that could be contrary to what the data monitoring committee is recommending.

I'd like to see some discussion of the possibility of a recommendation in these guidelines to give the data and safety monitoring committee a chance to--a kind of safety valve. In this case my suggestion is that if they're in strong disagreement with the sponsor that they be able to bring the disagreement to the FDA, that this would become part of a charter for data monitoring committees.

DR. LEPAY: Thank you. Any comments from the panel?

DR. SHOULSON: One thing is that the confidentiality agreement between the DMC members and the sponsor should not extend beyond the point that the data are analyzed because oftentimes these confidentiality agreements may extend 10, 20 years beyond that and whatever comes first, when the data becomes available members--either the DMC as a whole or members of the DMC--should be free to talk about that. And, of course, they should have the minutes available to document their proceedings.

DR. SIEGEL: I wanted to comment regarding the remark about DMCs being able to bring in disagreements to the FDA, that the guidance does state that if a data

monitoring committee makes a recommendation for a trial change based on safety concerns, that even if the sponsor does not make those safety concerns, that it is--and it uses the wording from our regulations--that the fact that that recommendation raises safety concerns that are of a nature that would normally by regulation require the sponsor to within 15 days tell us of that recommendation and its basis, and presumably their reason for not following it.

So that may help address some of those issues. We don't have any guidance--we steered clear of any guidance suggesting any type of direct communication between data monitoring committees and the FDA. However, we have in certain rare instances been contacted by monitoring committees and in other instances contacted monitoring committees. Throe are rare. When it's happened it's largely, I think, been useful but it's not something that we've specifically addressed or recommended and I don't think we have enough experience to draw general rules.

DR. LEPAY: Dr. Fleming?

DR. FLEMING: I think, Jay, if I'm interpreting Brent's comments, essentially he's stating concerns about confidentiality agreements that DMC members may have and regulations in DMC charters that would preclude even the

option that a DMC might have in the case of in particular serious ethical concerns, of conveying those concerns directly to the FDA.

My sense is it would be very rare when that would occur but I think if I'm interpreting his comment, he's concerned about that not even being allowed in those rare cases.

MR. DIXON: Dennis Dixon from the National Institute of Allergy and Infectious Diseases. I want to raise a question about something that Mary introduced in her presentation and then we heard about later, and that is the production of detailed minutes of the DMC meetings. In the guidance, the proposed guidance, there's even discussion that there should be sort of open and closed portions of those minutes.

For the DSMBs--DMCs--that our institute has worked with and that some of today's speakers are fairly familiar with, we have never kept such minutes. We produce written recommendations, a summary of the DMC recommendations, which are then conveyed to the steering committees and in some case to the local IRBs. But there's been no production of written detailed records of the nature described in the guidance that would be held confidentially until sometime afterwards. And when it's come up in the discussions it seems like it's sort of

obvious to the speaker or in the document why these are needed and I wonder if those reasons could be shared.

I know that it is a substantial amount of work even to get consensus agreement on the written form of the actual recommendations, which for any one study is less than one page. And the notion that we would produce detailed minutes that would then have to be circulated and get agreement by the members of the committees is daunting, especially if very few people are even in the closed sessions so that somebody on the committee would actually have to be taking these notes and producing these minutes.

DR. LEPAY: Mary?

DR. FOULKES: I'd like to address two words that you mentioned, Dennis--detailed and daunting. We don't intend to recommend something excessively detailed and certainly not excessively daunting but I know you and I have both seen minutes that are exceedingly terse. One of our panelists at one point in his life suggested that those terse reports out of the data monitoring committees should say "We met, we saw, we continue," and that's it. I hope I'm quoting him accurately. Am I?

I think that's probably a little too minimalist but there has to be something in between.

Okay, why? We've heard that at the end of a trial a lot of information is made available both to the

sponsor and to the FDA and we've also heard discussions of need for training, and so forth. In all of throe three contexts the entire process needs to be more visible than it has been during the closed and blinded period. There has to be some understanding and appreciation particularly when a new drug or biologic or device is being evaluated how we got there.

So basically that's--and there has to be something in between nothing and excessively detailed.

DR. FOST: Dennis, I would just say it's not uncommon that there are very contentious discussions about very important issues but that don't lead to a conclusion at this time to bring it to the attention of the steering committee. But if X happens or Y happens or depending on their response to an inquiry, we might change our view. Or at the next meeting we want to look at this very carefully again and comes the next meeting, we've all got our memories and everyone might disagree as to what it was we said we were going to do. It seems to me there needs to be some internal record of these very complicated discussions that nobody can remember six months later.

DR. FRIEDMAN: If I can make a plea for something that is not done often enough--Dave DeMets has done it a fair amount and a few others--that is after a study's over there ought to be a report, a publication of the

interesting issues so we can all learn from what went on in these studies. I don't mean airing dirty laundry but saying how certain kinds of decisions, difficult decisions were made. I think that will get at some of the educational aspects. Unfortunately there are very few such publications.

DR. FLEMING: Just very briefly, I think, Dennis, clearly what you've referred to is a very important element of the minutes, which are the recommendations and there's no controversy about that.

I've been very impressed in interacting in wide industry-sponsored settings that in those settings sponsors have been very consistent in ensuring that a process is in place to have documentation for open and closed sessions. It's not extensive, as Mary says, but it's the essence of what happened, a few pages. Someone is designated with that responsibility. It's very helpful to the committee and I think it's going to be very helpful and it is very helpful to the sponsors when the study is over, to be able to have access to what actually happened. And I believe the FDA should have access to that thinking, as well.

DR. LEPAY: Thank you. In the back?

MR. BRYANT: My name is John Bryant. I'm the group statistician at NSABP and probably my remarks should be interpreted in that light in that I feel that I have

some understanding of the cooperative group process and perhaps less so of industry-sponsored trials.

Nevertheless, I think this guidance, however it turns out, will have profound implications for the U.S. cooperative cancer groups. Most of the studies, as I'm sure you all know, that we conduct do have registration implications, at least potentially, so we're clearly interested in this guidance.

I heard it said earlier today that statisticians are a self-effacing lot and perhaps that's one of our big problems and I guess I'll attempt to dispel that notion a little bit here.

The first point that I'd like to, I guess, take some exception to is that the guidance is pretty clear that it's not intended to be proscriptive but rather it's supposed to describe generally acceptable models. And I guess I would argue that at least in some aspects the document is extremely proscriptive and I guess I'd like to read maybe two sentences. "The integrity of the trial is best protected when the statistician preparing unblinded data for the DMC is external to the sponsor. And in any case, the statistician should have no responsibility for the management of the trial and should have minimal contact with those who have such involvement."

Now one, I think, can reasonably agree or disagree with those statements but I think it's fairly clear, at least to me, that they're highly proscriptive statements. And I believe that if it's the intent of the drafters of this document to actually describe generally acceptable models and not to be proscriptive that perhaps some change in tone and perhaps in substance should be contemplated.

It's probably fairly clear that I do personally have considerable concern with the notion that a cooperative group data coordinating center, in essence, be blinded not only to efficacy data but also at least in some degree to safety data. And I guess I'd like to reinforce what I at least thin I've heard said by my friend Joe Constantino and Larry Friedman and Tom Lewis.

Some good arguments have been made here for blinding the statistician or blinding the coordinating center to efficacy aspects of the trial and to have results presented to the data monitoring committee through an independent statistician. Ultimately, though, I think there are some real down sides to that that have been articulated by others and I think that this document, in order to do what it's supposed to do--i.e., prescribe generally acceptable models, needs to pay some attention to

the real down sides of having data presented to a DMC by someone who ultimately is not very familiar with that data.

I have some experience in these matters. I've presented data for the NSABP for years to our data monitoring committees. I've sat on data monitoring committees both as, shall we say, nonparticipating statistician and I've also participated on data monitoring committees where, in fact, I have been the statistician who actually did the interim analysis. So I have some familiarity with these matters.

I have the highest respect for everybody I've served on data monitoring committees with. They're clearly a very highly functioning group. But I guess the bottom line is that the people who really know the trial best are within the cooperative groups who run those trials. If it is not our mission to objectively compare treatments in the U.S. cooperative groups, then I simply don't know what our mission is.

Now it may be that more attention does need to be paid to the issue of the degree to which the interim analysis statistician and the trial management statistician in some sense have to be separated. That's a good point that needs to be thought about. But I think the idea of trying to divorce the day-to-day monitoring of a clinical trial, at least in cancer, from a data coordinating center

is extremely dangerous. I think it will lead to diminished safety of participants and I really think that this is something that I think this guidance has to address. It doesn't address any of the down sides of divorcing the data coordinating center from the day-to-day conduct of the trial and I think it needs to do that.

DR. LEPAY: Thank you.

DR. SIEGEL: Those comments are certainly appreciated. I would perhaps clarify a point or two.

Nowhere does the document endorse the notion that the statistician who presents the data to the committee should be someone who is not familiar with the data, not receiving the adverse event reports on a day-to-day basis, not very familiar with the trial and its protocol issues that were implied or stated by a couple of comments, including earlier comments. It simply states that that person ought not to be in the employ of the sponsor or, if in the employ of the sponsor, ought to be completely separated from any role in trial management and then points out the cautions of how difficult such a separation can be and, in some cases, perhaps not feasible.

The only other comment I would make, because the issue was raised of objectivity and the coordinating centers being objective and also the issue was raised by Dr. Friedman's comments about NIH approaches and some

discussion about differences between government- and industry-sponsored trials, that a significant part of our concern here, as exemplified by the examples I gave, one of which involved the NIH, is not an issue of objectivity; it's an issue of how knowledge of the data can bias your ability to manage a trial.

I pointed out in my fourth example the rather considerable efforts the FDA makes in many of these cases to keep ourselves blinded to the trial. We consider ourselves quite objective but feel that once we know the interim data of the trial, when a sponsor comes to us and wants to make protocol changes and needs our approval to make them, we're going to be in a very compromised position.

So it's not because we're not objective but simply because we have that knowledge. So it's important to recognize that we're not impugning anybody's objectivity in any situation here, just trying to make people cognizant of concerns.

One final quick comment about that. That has to do with the issue of directivity and whether this is prospective or not.

In regulatory parlance, which I'm sure many of you are not familiar with, if we say something should be done we consider that nonprescriptive. It may be read that

way. So the quote that was read said the statistician should have no responsibility for the management of the trial. That is a nonprospective statement.

If we write a regulation, we don't use that word. We say the statistician must have no responsibility. In that case if you do it, you can get in trouble, even if you have the world's best reasons. If we say they should have no responsibility, what we're saying is what you're thinking, that here's all the reasons why they shouldn't and we think in general they shouldn't but, in fact, there may be in specific cases reasons that are even more compelling why they should and that can be quite acceptable. And if you're willing to bear the risks to the trial that this talks about and to take those approaches and to try to minimize those concerns, those are considerations.

That's why this is a guidance. Perhaps we can make that a little bit more clearly. It's not intended to be prospective in the sense we think of being prospective, which is to say you don't do it this way and you're automatically in trouble. It simply says this is a way that we believe is consistent with our regulations and a good way to do it. However, there are other ways. If you choose to do it other ways you ought to have a good reason

for showing why and how those are consistent with regulatory requirements.

DR. LEPAY: Dr. Fleming?

DR. FLEMING: Just briefly, certainly it's extremely complex and controversial as to how you optimize these goods. One good is knowledgeable oversight and the other good is independence to achieve maximal integrity and credibility. And no one, I believe, is advocating that we give up knowledge for independence. What we're talking about is ensuring that individuals who are on monitoring trials are knowledgeable.

I'm director of a stat center so I have the hat on frequently of turning our studies over for monitoring by an independent committee. I don't believe that because I'm the lead statistician on a trial that I'm the only one who can be highly knowledgeable about issues that are extremely important in the monitoring of that trial.

Clearly the people we have on monitoring committees and the liaison statisticians must be chosen to be very knowledgeable people but we also augment that insight that they have by open sessions, as are advocated here in the guidance document. Open sessions allow for further sharing of insights by those individuals who have unique insights who aren't also members of the data monitoring committee.

So the entire structure is intended to achieve this balance between knowledgeable oversight and independent oversight.

DR. LEPAY: This is an important issue. Dr. Fost?

DR. FOST: Jay, with all respect, we've gone through now--we're in the middle of a six- or seven-year period when OHRP began issuing guidance documents of incredible detail, not regulations, arguably even tolerated by the regulations, about which there's terrible disagreement and, as you know, major institutions have been shut down for months at a time not for deaths, not for adverse events, but because of failure to comply with guidance documents. Which is not to say that--

DR. SIEGEL: Not by the FDA.

DR. FOST: Not to say that the FDA would ever do such a thing.

DR. SIEGEL: We wouldn't.

DR. FOST: Well, with all respect again, there have been instances from the FDA. Stanford some years ago was almost threatened with a shutdown because of things its IRB were doing. I mean it got very stern letters from the FDA that, as I was saying--

DR. SIEGEL: Oh, we'll shut down trials, sure, but not for noncompliance with guidance documents. Noncompliance with regulations.

DR. FOST: As an IRB member and as any dean of a research center, to not comply with guidance from a federal agency these days is to risk having your entire university shut down for months.

MR. CANNER: Joel Canner, statistician with the FDA practice group at Hogan & Hartson in Washington.

I applaud the FDA for the very detailed and comprehensive description of the form and function of DMCs but I'm trying to figure out how to apply this to the companies that I work with, which are by and large small device manufacturers. These companies typically do small studies that may or may not be controlled, may or may not be randomized, concurrently controlled, and so forth, often not even possible to single-blind them, let alone double- or triple-blind. There are often cost restraints and companies typically manage their own trials without the help of an outside CRO or other agency.

All that having been said, many companies of their own volition decide that they need a DMC or perhaps the FDA insists on it and the question is in establishing a DMC do these companies in these situations need to buy into all the many detailed aspects of this guidance or is there

a sort of DMC lite for these trials that don't fit the large multi-center long-term heavy duty trials that the pharmaceutical industry engages in?

DR. LEPAY: Excellent.

DR. CAMPBELL: I'm Greg Campbell from CDRH.

I think you raise a very important question and one of the things I did not mention this morning which perhaps I should have are questions about when a DMC may not be mandated or may not be recommended and there are certainly lots of examples that you and I can come up with where the trials are small, where the length of time is short. I mean if you can go down the list of all the questions that I posed this morning there are lots of situations where it's not clear that a data monitoring committee, in and of itself, adds a lot of value to the trial.

Having said all that, there are still some advantages that companies might see in having a data monitoring committee, especially having to do with being able to look at the data on an interim basis and perhaps stop early for reasons having to do with effectiveness or perhaps even safety.

Having said all that, I think that there are probably other models than the ones that are set forth in this document and this is guidance, it's only guidance and

we don't want to discourage people or companies from coming to us with other ways of thinking about things.

DR. LEPAY: Thank you. We have about five more minutes and three people standing. I'd like to see if we can address those comments. There's another open discussion session at the end of the next panel.

MR. CONSTANTINO: Joe Constantino from the University of Pittsburgh and the NSABP and I'll just be very quick since I did speak this morning. I'm hearing from the panel things that I'm glad that I did come to hear because they're saying things which are not reflected in the document.

Dr. Fleming, I just heard you say there is a give and take between the drive for independence of a statistician and the safety. That really doesn't come across in the document. That might be the intent but it comes across very loud and clear that everything is for independence, that it's all one way.

Dr. Siegel, you said that you're not driving to say that the statistician has to be independent of the sponsor, has to be isolated. Your document doesn't say that. Your document says very specifically it is best that the statistician preparing the data be external to the sponsor. Now if you said that--I mean I don't see how someone could be in a cooperative group--some statistician

who has to be involved with the data day to day who then can transmit it to the data monitoring committee cannot be considered part of that sponsor by the definition of what you're calling a sponsor.

So to me there's a conflicting thing. You have to be paid by somebody to be there day to day to see the data and that's going to be the cooperative group, no matter how you look at it. You can say this guy has the office all by himself in a separate building maybe but that doesn't come clear. You say he has to be external of the sponsor and I think some wording into the document to make it clear that there is a give and take and that there are alternatives is what's needed.

And just one last question, to reiterate how we are focussing on independence versus what the real issue of what we're doing is all about. Dr. Siegel, you gave three very good examples of things that should not happen in clinical trials. They have had nothing to do with whether or not the statistician knew the treatment codes of the unblinded data. They were poor science and poor clinical trial design.

The first one was there was no up-front data analysis plan well defined and it was tried to be changed in the middle of the trial. You don't do that. That's poor statistics. You don't do that.

The second one was dealing with changing end points in the middle of a trial. You can't have a primary hypothesis planned a priori before randomization if you change it in the middle of a trial. You don't change the end points. It's that simple. You can't do it. It's poor statistics. It has nothing to do with if you know the blinding or the unblinding.

The last one was changing the sample size to increase the power. Again you can't change the primary hypothesis. It's based on some set power. You can't change it after the fact. You can increase sample size to maintain the power because perhaps your hazard rate wasn't what you thought it was going to be but you can't change the sample size to improve your power. Poor statistical design.

If you have an up-front, well designed and specified analytical plan, if you have an interim monitoring plan that's well specified up front, all those kinds of problems that you gave as examples go away.

DR. SIEGEL: I would just quickly say that in all of those examples sure, things might have been planned better but nonetheless, in those examples and in many examples we see, it simply is not true or correct to state that end points shouldn't be changed, sample sizes shouldn't be changed, trials shouldn't be changed.

Trials take a few years to conduct. Over the course of those few years other trials get completed with the same drug, you learn about the appropriate dosing of the drug, you learn new information about adverse events, you learn about competing drugs that need to be incorporated into the trial. There is an imperative, to protect patients and to do good science, to be able to change trials in mid-stream. It is part of good trial design and it is best, indeed it is only accomplished without bias if it's done by people who are not biased by knowledge of internal information.

Secondly, on the question you raised of balance, we need to look at the balance of the language in this document. I think the point is perhaps very well taken. It's certainly been taken by many people that there isn't a discussion, as much discussion about the issue that the statisticians and others be knowledgeable of the trial and its design and I would suggest that the reason that's not there is that we've seen several trials have regulatory failure because of these sorts of lack of independence, and that's an important message to get out.

We can try to improve the balance but I do want this audience to know that--I certainly appreciate the comment, too, that we can say something's not binding and it often gets interpreted as being binding but it is not

binding; it's here in the language right after the sentence you quote that says "The integrity of the trial is best protected when the statistician is external to the sponsor" is a statement. "In any case, the statistician should have no responsibility for the management of the trial." That certainly acknowledges that they may be part of the sponsor but should not be responsible for management of the trial. The statement that they should not doesn't mean that they cannot; it means that they can but if they do, as it says right at the beginning of the document, "The intent of this document is not to dictate the use of any particular approach but rather, to ensure wide awareness of the potential concerns that may arise in specific situations."

So there's not much more that we can do to say that it's to raise your concerns and alert you to problems and it's not binding than to write that in several places in the document. We can try to write it in a few more places in the document; maybe that needs to be done. But that is, in fact, the intent and that is, in fact, the way the document will be used.

No IRB will be shut down and no company will be shut down because the sponsor's statistician or the data center statistician was part of the monitoring committee. However, if that statistician was involved in proposals to change the trial, those proposals may not be looked

favorably upon or the trial, if changed with knowledge of interim data, may be viewed as invalid. That's a reality; that's what this document is trying to alert you to.

DR. LEPAY: Dr. Fleming very quickly?

DR. FLEMING: I'll try to be real quick.

Not all studies are confirmatory but those studies that that are confirmatory, I'd like to be able to interpret them in that manner. It means, as the speaker was saying, I'd like to have a prespecified hypothesis that I then confirm.

At the same time, there can well be during the course of a long trial external information that could enlighten us as to what the hypothesis really ought to be. I actually don't have a problem if I'm certain that it's external data that leads to that refinement and this is the essence of where this independence and separation enables or empowers the sponsor to have that flexibility.

The other aspect is judgment is inevitably always going to be necessary. It's not unique to us here in monitoring committees that we want our judges to be independent, unbiased. That's true of any judge in any setting. So the concept of having an independent group of individuals who have sole access is simply our attempt to implement concepts that are widely recognized in many other areas.

DR. LEPAY: Thank you.

Again I'd like to thank our panel and those participants from the audience. A round of applause.

[Applause.]

DR. LEPAY: And we have a 15-minute break scheduled. We'd like to convene promptly at 3:30 and we'll proceed to Bob Temple's talk.

[Recess.]

DR. LEPAY: Thank you very much. We'd like to move on to our last series of discussions, the final two sections of the guidance document and our third panel for the afternoon.

So to initiate the discussion I'd like to introduce Bob Temple, who's director of the Office of Drug Evaluation, one, and associate director for medical policy in the Center for Drugs. He's going to be providing us with information on Sections 5 and 7 of the guidance document.

DMCs AND OTHER REGULATORY REQUIREMENTS

DR. TEMPLE: Thanks, David. These are relatively short, not very detailed or very directive sections, so this will be fairly short and we'll have lots of time for questions.

Section 5 talks about data monitoring committees and regulatory reporting requirements. That'll be short

because data monitoring committees mostly don't have regulatory reporting requirements. And sponsor interactions with FDA regarding DMCs. Then I'm going to add on a little extra topic, which you'll see when I get to it.

There are really two sections of part 5, one about safety reporting, one about expedited development. Under the heading of safety monitoring it's important to distinguish two kinds of adverse events or potential adverse events. One is the obvious thing--a patient dies of acute hepatic necrosis or has agranular cyrtosis or aplastic anemia, something like that. You don't need a data monitoring committee to interpret those events. They speak for themselves. In fact, the sponsor, if those were not known to be problems, has to report such events within seven or 15 days. And in almost all cases the sponsor chooses to take responsibility for that on its own.

These are relatively obvious, easily recognizable, not part of the normal history of the disease. There should be very little confusion. If that's not true then that's another question.

They can be submitted to FDA blinded or unblinded and some people like to keep them blinded but I frankly have never understood that so maybe that's something we can talk about. I don't see how a case of agranular cyrtosis

unblinded interferes with the study. And, as I said, it's usually submitted by the sponsor.

Their responsibility to do that is so urgent that unless the data monitoring committee meets very often they would violate their rules if they put it through the data monitoring committee, but they usually do not.

It's worth noting and the document notes this, that such serious unexpected--that is, things not in the investigator's brochure--adverse events are reported to FDA and to all investigators, who then under various other sections of the rules--not guidance, rules--have to report them to IRBs.

There are cases in which direct reporting to IRBs by the data monitoring committee or the sponsor have been arranged. For example, if there's a central IRB that's not a bad idea, but that's not required.

A second whole category of adverse events and one much more appropriate to consideration by data monitoring committees are events that are part of the disease process or relatively common in the study population. Heart attacks in a lipid-lowering trial, even if heart attacks aren't the end point, will be something that would be common in the population. It would be hard to look at a single event and know whether it meant anything or reported

anything or should be reported. Death in a cancer trial and other things that are either common or expected.

In this case it's very difficult to assess an individual event and the data monitoring committee role is crucial because you need to look at the rates and make some determination about whether the rates are worrisome or not worrisome. They therefore need to be done by a party that is neutral, that doesn't have a bias, because judgment's involved and we want our judgments to be unbiased.

This almost always would include events that are the study end point--that's sort of obvious--but other serious events that are relatively common in the population and sometimes what you have is a greater than expected rate of a recognized adverse consequence of the drug--for example, bleeding with a TB3A inhibitor. The rate might be higher than you expected, even though you knew that there were going to be some.

The document notes that this is sort of an opinion about a regulation but it's only guidance.

A data monitoring committee request for a safety-related change in a protocol, such as lowering the dose to avoid toxicity or change in the consent form to warn of an emerging safety concern would be interpreted by us as a serious unexpected event and therefore reportable to the FDA by the sponsor or by the data monitoring committee if

they've made that arrangement. So these are obviously important; it's a relatively unusual thing.

The second reporting requirement that's described is expedited development and this, as anyone who reads it will note, is a somewhat vague section because this doesn't happen very often, we're not too sure what the track record tells you and in general, FDA interaction with DMCs is not a thing we try to promote because they're supposed to be independent and for various reasons it's potentially a problem for us.

However, we do note that where we're really interested in a serious and bad disease we may be more than usually involved with the progress of trials. Therefore if any interaction with the data monitoring committee is anticipated it's very important to try to dope those out ahead of time.

Again we expect that FDA access to unblinded data is going to be a very unusual thing. First of all, as has been touched on, knowing interim results would keep us from advising independently on changes in the protocol, just as a sponsor would be unable to do that if the sponsor knew the data, and I would say just as a DMC would be unable to do that if the DMC knew the data.

The other reason we're careful about learning early results is you can get a sort of public health

tension in either direction. You know, we're the government; maybe we should stop this awful thing. We believe we know of at least one example of where a study was stopped probably prematurely because we got nervous and we'd rather not be exposed to that. That's why they pay the data monitoring committee members all that money.

There's also a potential for a very damaging premature judgment. That is, if we tell a company oh yeah, you've got to stop now, and then we look at the data more closely and half of the cases turn out not to be really heart attacks or something, we're in a very difficult position when it comes to reviewing the data.

So for all those reasons we generally don't like to do it but there have been cases where we did. We were reviewing a drug for adjuvant breast cancer chemotherapy and it showed clearly superior response rate and time to progression. We wanted to know before we approved it that at least the mortality wasn't worse. The mortality results weren't mature yet; they were still under development. And we were able to work with the chair of the data monitoring committee and receive assurance that it at least wasn't going the wrong way. That may seem small but it was a big step to us. We worried about it a lot.

This is a very odd, recent case. A sponsor wanted to consult us on whether to make the primary

analysis the whole group under study or a subset of the group that was started somewhat later with an additional treatment. And they'd actually been advised by their DMC that they should look at the latter. We thought the DMC was in full knowledge of all the study results, both of the subgroup and the total, but today's been a learning experience and they, in fact, were not at the time they gave the advice. But in seeking the advice--and this isn't the company's fault; it's because we asked for it--we obtained the data that had been presented to the data monitoring committee eventually that showed the results using the whole study group or the subset, and the company's now coming in to ask us which they should do.

Well, of course, we couldn't tell them. We were contaminated. So obviously they hadn't thought about it, for sure we hadn't thought about it, but it does turn out the DMC had thought about it, even though at the time I wrote the sidle I didn't know that.

So there are major disadvantages and care needs to be given when we see interim results. It really restricts us.

But, of course, just to add to that, and I forget whether this is on a later slide or not, we will--oh, yeah, this comes up again.

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Now a somewhat overlapping question is sponsor interactions with the FDA regarding how to set up a DMC. It would probably be very useful to discuss data monitoring committees with us but I have to say that it's not common to have those discussions with one exception, and the exception really isn't about the data monitoring committee; it's about stopping rules, which, strictly speaking, is about the protocol, not the data monitoring committee.

But what we could consult on is planning the data monitoring committee, what its role is going to be, who's going to be responsible for what kinds of adverse reactions. We might comment on the members, although we don't like to identify particular individuals. That makes us nervous but we might talk about widening the membership to include someone from South America or whatever seemed necessary or bona fide, well trained, properly constituted ethicists.

So those are things we do think about and it would be worth discussing those matters. Probably in some cases we'd tell people that we didn't think they needed one, which might save people trouble, too.

We are very interested, as has been discussed repeatedly now, with how the group performing the interim analysis would be protected from other parts of the sponsor. I won't go into that further but obviously it's a

point of great interest, however it gets resolved. And we'd certainly be interested in participation of the sponsor at meetings. Again as has been discussed at length, we didn't try to set a rule but we did note that certain things are potential problems.

And, of course, there's been some discussion of this. I guess I think interim analysis plans or stopping rules are something that should be developed by the sponsor and presented to the data monitoring committee, who can then respond with "This is stupid," or something like that, but it's basically part of the protocol. At least that's what I think.

Any intent by the sponsor to access interim data is a major step and should certainly be discussed with FDA in advance. The one case where this will be expected, of course, is in association with a recommendation by a data monitoring committee to terminate a study. At that point the reasons have to be given and the sponsor will see the data.

A recommendation to terminate a study for success puts the sponsor in a difficult place. First of all, they like the idea and hope that we will, too, but sometimes you pay a price for these things and we would certainly want to at least think about the adequacy of the safety data, whether the study has been stopped so quickly that we don't

really know what we needed to know about the duration of benefit, whether we're uninformed about critical subgroups or whether there are funny things in there that are a problem. And, of course, you often don't know much about secondary end points.

The trouble is it's hard to do all that with a proposal to terminate the study in hand and all of those things should have been considered earlier, if possible. We often, for example, recommend that studies not be stopped except for survival or some other major event kind of benefit because you end up with a tremendous loss of data and a less convincing protocol. So those are all good things to discuss before the committee launches a recommendation at you.

Of course, if there's a recommendation to terminate a study for safety, that would always require an FDA submission. There would obviously be implications regarding on-going studies and we'd certainly hear about all that.

There are lots of things a data monitoring committee could recommend in the way of protocol changes and some of those would have little implication with respect to approval but some of them would. Changes in end points could lead to an end point that was no longer considered reasonable. Changes in permitted concomitant

medications or in dose or schedule could cause problems in interpretation. I don't have examples of those but they could.

But most important and I don't think it's emphasized in the draft enough probably, the unblinded data monitoring committee really can't credibly change end point, sample size, subset plans or anything, any more than an unblinded sponsor could, without at a minimum affecting alpha or introducing bias that we don't know how to correct. That probably needs some discussion.

Okay, now for something completely different. Sections 4, 4.15 and 4.42 refer very briefly to a possible different kind of data monitoring committee and some of the discussion today has gone in this direction. I actually first, even though these things have existed for a long time in actual fact, the first time I heard anybody talk about it at length was at a meeting at Duke that Rob Califf had set up and someone from Lily said oh, we set up data monitoring committees to look at our whole program. We get wise heads together, people from outside not so invested in a particular approach and we find that very useful.

So this sort of thing, which one might call DMC type 2, isn't developed to monitor a single large trial but rather, to observe an entire developing database, obviously looking at safety across the whole database but also

thinking about how to design the new studies, whether special monitoring ought to be introduced to worry about something, whether there ought to be special tests, and even to look at potential advantages or disadvantages that might be explored in studies.

This differs in a lot of ways from the more usual type. First of all, I think the principal expertise is in many cases clinical here and that's different because despite their modesty, we know that biostatisticians are incredibly crucial to the data monitoring committees of the other kind.

I believe you could say that complete independence from the sponsor is not as critical here. We're talking about descriptive things. It's perfectly reasonable for them to argue with each other. You don't really have to be blind to think about what the next study ought to do or whether you should design it differently. But it does seem particularly useful to have a strong external element, first of all, to obtain additional expertise if you need it but also some needed freedom from past obligations and assumptions, a little independence of judgment.

As I said, this focus is on the whole database, not on single trials. It's especially helpful in a high-risk population where looking at a bunch of trials may

start to reveal things that are not obvious from a single trial. Our past model for this might be FIAU but there are many cases where things sneak up on you that aren't obvious.

Such a group could pay attention to developing effects and subsets so that instead of being dismissed at the time of approval they'd actually be studied and there'd be real data on them because somebody planned a test for them. So there are a lot of opportunities.

It is worth noting that this whole idea would work best in a situation of what might be called rational drug development, where one study informs and modifies later studies. That is the way people sort of used to do it but it's uncommon now to see that sort of leisurely pace of drug development. What you see much more commonly now is a couple of phase II studies to make you think there's a drug and then phase III all at once.

So the burden there, since you don't get to learn from the results of one study in planning another, is to try to build all the variety into phase III that you can, and I would not say that's commonly done. But an outside advisory committee, thinking broadly about this along with the company, could think about studying a wide range of severities, could be sure that they're looking at the appropriate dose and dose interval, looking at appropriate

combinations with other drugs, making sure that an adequate duration of trials has gone on, thinking about randomized withdrawal studies. The whole idea is that not just the company alone but the company with some help would be thinking about the whole development program.

Section 442 about early studies proposes something not so different from that but for a special case and that is a case where there's high-risk drugs and where the investigator has a potential conflict of interest. In that case the data monitoring committee or even a data monitoring person, as I think someone said, may enhance the credibility of these efforts, especially when there are important ethical dilemmas involved.

It's just worth making one last point. There's a tendency to try to get perceived problems in an environment addressed by the groups that seem to be functioning well so there's a certain tendency to want data monitoring committees and also to some extent FDA, I have to say, to solve all the problems because they seem to be able to do their jobs pretty well.

Well, that doesn't work. You won't learn about an important adverse effect unless the investigator reports it. It won't go to an IRB, it won't go to a data monitoring committee, it won't go to FDA unless someone recognizes that coughing for a week isn't an intercurrent

illness but is a response to an inhaled drug. So a canny investigator, a well trained investigator, can't be substituted for by a data monitoring committee. Having said that though, an external person could help an alert investigator interpret what he or she saw and might be useful.

So that's the end of my advert.

DR. LEPAY: Thank you very much.

I'm going to invite our last set of panelists to come up if they would and our AV people again to help terminate the slide presentation here.

I'd like to introduce the members of our panel. Michaele Christian, who's associate director of the Cancer Therapy Evaluation Program at the National Cancer Institute of the NIH. Dr. Robert Califf, who's associate vice chancellor for clinical research and director of the Duke Clinical Research Institute, professor of cardiology in the Department of Medicine at Duke University. Dr. David DeMets, professor and chair, Department of Biostatistics and Medical Informatics from the University of Wisconsin. Dr. Bob Levine, professor in Department of Medicine and lecturer in pharmacology at Yale University School of Medicine and author of the book "Ethics in Regulation of Clinical Research." And Dr. David Stump, senior vice

president for drug development at Human Genome Sciences, Incorporated.

And again I'd like to use the same format we've had throughout the day and ask if Dr. Christian would like to begin by making a few remarks.

DR. CHRISTIAN: I have to confess that I arrived late because I had some competition so I wasn't familiar with the format but I do have a few remarks.

I wanted to point out some areas that I think probably merit some additional discussion and I want to put this in the context that the Cancer Institute as a sponsor sponsors over 150 phase III trials at any given time, so we have a large number of trials on-going and our collaborating sponsors, if you will, the multi-site, large cooperative groups that do these studies, may have 20 trials on-going at any one time, phase III trials.

So the model that we've used for data safety monitoring boards for all of our phase III trials for many years is that each group has a data safety monitoring board which overlooks all of these trials. So it's a little bit different than the flavor that I got from the guidance, which was that it dealt primarily with DSMBs for large single trials and I think that's probably something that one might want to comment on in thinking about this.

So that has some practical implications and while clearly our DSMBs follow most of the principles outlined here there are some significant differences. And I think that we need to think a little bit about not creating excessive burdens for DSMB members that are already covered by other reviewing bodies. For example, there are suggestions that protocols and consents and analytic plans and other aspects of protocols be reviewed before studies are initiated by DSMBs and I think that actually bears some discussion.

At any rate, other issues that I think are important here are that there was, I think, for us some confusion about the role of the DSMB versus the IRB, the institutional review board. And again I think part of that related to this issue of initial review of the consent, the protocol, et cetera. So there's some confusion, I think, about the relative responsibilities of those two bodies, both of whom have patient protection as a primary focus.

Another area that I think could stand some clarification is the role of the FDA for non-IND phase III studies. We sponsor quite a few important phase III studies that are monitored by DSMBs but are not done under INDs, so the role of the FDA and the advice and guidance for some of those, I think, is important.

You're laughing, Bob. There are some appropriately done that way, I think.

Finally, I think an area that probably also bears some additional discussion is the responsibility for toxicity evaluation. I think that this is pretty complicated and DSMBs, of course, usually meet every six months or so and the responsibility for on-going toxicity monitoring by the study team and the need to potentially see comparative toxicity data in order to exercise that responsibility carefully I think is something that bears further discussion.

And similarly, I think the sponsor, which can put comparative toxicities in the context of a larger toxicity experience and database, is an important issue. I think they're well positioned to monitor safety in an on-going way.

So I think those are the major points that I wanted to bring out.

DR. LEPAY: Thank you.

Dr. Califf?

DR. CALIFF: I guess I'll play my usual role and just take a few potshots at everybody here to see if it raises discussion.

First of all, I will say I think this document is a major step forward, interpreted in the right light, which

is that it is a set of recommendations which anyone could logically disagree with individual points and come up with better ways of doing things. So unless it's written down and generates discussion, we're not making progress, so I'm really glad to see this being done.

I'll just start with our federal friends. In general I would characterize the current environment as federal chaos and widespread panic. The federal chaos is that we don't get the same guidance from the FDA, the OHRP, the NIH and the IRB in their interpretation. And as Ira Shoulson said, at the most fundamental level a human experiment is a contract between a patient and either a doctor or someone else who's providing medical care and the widespread panic is coming from our IRBs, which are responding to the federal threat of institutions being shut down by going to the most onerous common denominator.

So the agency that has the most onerous demands is going to win out in terms of what gets done and it's dramatically increasing the cost of clinical research and slowing it down in the U.S., which I would argue is not good for patients.

So the good news about the emphasis on protection of human subjects, the interaction with the FDA and others is that more money is being spent on protecting of human subjects. The bad news is that probably most of it is

being spent on the wrong things and I know a lot of people on the panel agree with that assessment. What to do about it is a different issue.

Secondly, we have a real international problem which I don't think has been addressed here, which is that FDA and the European regulators and the Japanese regulators don't agree, particularly on issues of adverse events and how to deal with them. And for those of us who do large international trials, there are really major problems that arise because you can reach a great agreement with the FDA, for example, on a more streamlined approach to a clinical trial, and then it becomes the most onerous country that rules the day. So if Germany says you've got to have every adverse event reported in real time no matter what it costs, then that's what companies have to do and the associated investigators.

So despite all the efforts at harmonization, this is an area that needs considerable work in terms of the interaction.

Third, I'll just take on the company regulatory groups and pharmacovigilence groups, which everyone is scared to death of because a word from them inside a company and it's a major problem, and I think there is a need for a better--I don't know how to do this but better dialogue between the good intentions at the FDA in

particular and the regulatory groups. It seems to me that it's hard for that to happen because of the interactions that can lead to the negative repercussions at times.

So this relates to data monitoring committees because there is a sort of semi-independent activity that's been referred to of adding up and calculating adverse events. Let's face it; at least in large clinical outcome trials if you've added up the adverse events you often have the answer to the trial in real time and I don't know of any way to get around this except devising rules which have the adverse events go through an independent organization. And yet, as was pointed out by a questioner already today, if the ultimate responsibility lies with the company, we have some guidance here which may be in a bit of conflict.

Then finally, the NIH I'll get on for not investing enough money in studying how clinical trials should be done. Despite the fact that we do them all the time we're still left mostly today with people's opinions based on anecdotal experience when there's enough empirical evidence now about a lot of what should work and what shouldn't that if there's just a little bit of funding relative to what goes into other things at the NIH in studying how to do it better, I think we would do better.

Now as relates to this complex interaction, just an observation I'd have is that there seem to be three

views of what clinical trials are. The one that we're most afraid of, I think those who do it professionally and have studied it, is the so-called engineering approach, which seems to be rampant mostly in company executives and sometimes in people at the NIH who want a public health answer to come out a particular way.

What I mean by engineering is the goal is to get a result in the trial and the purpose of monitoring is to steer the trial to get the result that you need. Although people may deny this happens, my experience is it frequently happens and part of what we're trying to do is protect against that.

The second would be to regard the trial as an inanimate immutable object and that was brought up by a person already today, that you're stuck with what you started with and that actually would take care of almost all the problems we've discussed today if you did it that way but I would agree with Jay that it just brings up a whole new set of problems of you can't ignore external evidence and things that change. So I would advocate that a trial is a living organism that has to be nurtured and fed, requires a lot of judgment. It can be changed but it has to have a set of rules that everyone agrees to and I think this document is a good start in that direction.

So I've taken a few potshots. Hopefully Dave, as usual, can straighten of the things I've said.

DR. LEPAY: Thank you.

Dr. DeMets?

DR. DeMETS: I've been trying to straighten out Dr. Califf for years but I haven't succeeded.

I think that this document is a step forward, as Rob said. I think the Greenberg Committee would be very proud of where we are but they might wonder why it took us 35 years to get here. Nevertheless, I think it's a major step and it will be a living document which will change over time.

Over the course of today I wrote down a few things that struck me as issues that I just wanted to comment on. When I look at a data monitoring committee I think it has several priorities. One is to the patient, two is to the investigator. At some distance--there's a gap--the next would be the sponsor and lastly would be the FDA.

If you're looking at a trial which has an outcome that's not mortality or major irreversible outcome, such as hospitalization or death, and at the halfway point you see a 5 standard error result, you've met the contract that you have with the patient and what concern, if any, should the monitoring committee have about the regulatory implications

of terminating that trial early? I don't know but I think it's a tension that happens in many trials and it seems that the answer lies somewhere in what the informed consent says about that kind of situation. So I think we need some guidance about those because they do happen.

Second, the quote about we met, we saw, we continue, was not about the minutes of the meeting but what we should tell the IRB and the sponsor. I think we do need to have minutes that are at least summaries. I don't think we should have transcripts or detailed minutes. I think that almost inhibits free discussion.

Finally, not finally but some additional what I would call myths. One is DMCs are expensive. I think that's ridiculous. I think they're a small percent of the cost of a total trial. If you assume you're going to be monitoring data at all somebody's got to do the monitoring and prepare the reports. The added cost of a data monitoring committee is quite small in the context of the trial and you get a lot of benefit from doing it, as we've heard about. So I don't think we should burden the data monitoring committee issue with the fact that it's expensive. There's some expense but it's relatively small in my experience.

Another myth is that the FDA demands a monitoring committee to be blinded. I hear that a lot and, as you've

heard today, that's necessarily true. It doesn't say that anywhere. In fact, it's encouraged to not be blinded. But that's something that is said over and over again by sponsors and it certainly adds complications to the monitoring committee's way of doing business.

Another myth is to minimize the number of interim analyses, to do as few as you can get away with. That seems to be moving in the wrong direction. Your job is to protect the patients and the investigators, as I said, but it's something that is quoted.

Another myth is that you must follow a rigid schedule, no deviations, no change of analysis plans. Obviously a monitoring committee must respond to the situation it sees, so that it cannot follow exactly always a rigid schedule or the analysis that was laid out in some set of tables at the beginning.

Finally, the issue of the benefits of an independent or external statistician. There is the issue of the firewall, which we've talked about, but another issue which I think is almost more compelling is that when studies are done and completed, it's amazing to me how quickly for negative studies or neutral studies staff at sponsors are reassigned to new projects. The investigator therefore and the investigative team is left without any access to the data. And if they're in any academic

environment they want to publish the results and if that happens, even in the best of companies, resources are limited and staff get reassigned.

So one added benefit to having that external statistician and statistical center is that while the sponsor may reassign their staff for better promising results, the academic community can still have access to the data and publish it.

My final comment is this process is not new. We've been practicing it for 30 years. We're getting better at it. Maybe we'll get it right. But as it evolves I think it has a very good track record and yes, there are variations but overall I think it's served us very well in the past 30 years and I think we should strive to always improve it, but I think it has a great track record.

DR. LEPAY: Thank you.

Dr. Levine?

DR. LEVINE: Thank you very much. I've also taken some notes in the course of the day and have picked out a few favorite comments to make.

I would like to begin by saying that the guidance document that we were asked to respond to is an outstanding document and those who know me well will have trouble recalling the last time I said that about a federal document.

I particularly appreciate Susan Ellenberg's starting us off with a list of definitions. I want to recommend two more candidates for definition. One is the word "equipoise." I have heard the word "equipoise" misused at many, many meetings, including this one. Those who want to use this word should look up its definition.

And the second most commonly misused word is "dilemma." We very rarely encounter bona fide dilemmas in data monitoring but sometimes we do, but we've heard dilemmas discussed as if they were part of the routine business of a data monitoring committee.

I think the document does a good job in recognizing the different styles of data monitoring that are necessary in different contexts. Thinking about that haws caused me to reflect on the assignments I've received as a member of a data monitoring committee from various agencies, both federal and in the private sector.

I think almost invariably the data monitoring committee is asked to monitor for patient safety, sometimes to the exclusion of anything else. That's a very important role for the data monitoring committee and it gives us many important trade-offs in the overall system for human subjects protection. I'll mention one of those in a minute.

Or secondly most commonly, the data monitoring committee is asked to monitor the actual collection of data. Are the case report forms being returned completely and in a timely way? Is one center doing a little bit better than another in getting in their paperwork? This is not a rewarding function. I think basically you could do that function very well by hiring the people who are about to become unemployed as the airport security people are replaced by federal agents.

I think it's very important that somebody keep track of whether the cases are being reported properly and in a timely way and I think it would be good to take the summary of their findings and turn that over to the data monitoring committee, which should have the expertise to tell whether or not some deficits in the monitoring process or in the reporting process could be detrimental to the conduct of the trial.

I think the thing that the data monitoring committees are called upon least to monitor is that which they're best at, and that's efficacy. The reason we're concerned with a lot of this blinding and so on has to do with the implications of efficacy monitoring and particularly taking interim looks at efficacy data and I would like to see that made the largest role for the

typical committee and have that role emphasized in whatever guidance documents might be issued.

Now a second point I want to make has to do with the interplay between various agents and agencies in the human subjects protection system. One of the things, I was very sympathetic with Dr. Califf talking about how IRBs are responding to things that university administrators are heaping on them based upon their reading of the requirements of federal agencies in the newspapers, usually shortly after a major institution has been closed.

One of the most onerous and least productive things they've been asked to do is to conduct periodic approval or reapproval of protocols at convened meetings. To show you how senseless this is, shortly after there was a report or shortly after there was a survey of all of the reports from then OPRR on closing various research institutes or research establishments in universities, somebody enumerated what was mentioned most frequently and found one of the two most frequently mentioned things was failure to conduct annual reapproval at a convened meeting. At a meeting not too long after that I told what I thought was a joke, that my university had responded by buying the IRB two shopping carts to transport all of the protocols to the convened meeting and when I said that, smiling, two

other people from other universities said they had exactly the same experience.

I think that reviewing the adverse events that are reported worldwide to every IRB that's involved in reviewing research connected to what might be called a test article is probably the least fruitful, the lowest yield activity that the IRBs get involved in. They are certainly nowhere near as well equipped at doing this as the data monitoring committee. And I think the data monitoring committee has the special advantage of when they're looking at all of these adverse events they also have denominator data, which the IRB never has.

I think part of the trade-off here should be that the IRB should only be asked to look promptly at reports of adverse events that occur within their own institution and then only those that are both serious and unanticipated. I'm often asked why should they even look at those and the main reason they should look at those is because some people in their institution don't understand what the requirements are for passing this information over to, for example, the Food and Drug Administration and the sponsor. So that's part of the purpose of having them review these. Also, sometimes they will find something peculiar in the local environment that could account for an adverse event, which may not have been apparent to the investigator.

There's many, many understandings of how best to use an IRB. We've had frequent government reports saying that the IRBs are overburdened, overworked and this threatens their effectiveness but every time we see such a report the recommended remedy for the problem usually entails increasing the burden on the IRB. Enough of that. We're not here to discuss the IRBs' problems.

I think if I had to make one major editorial correction in the guidance document it is that at several points reference is made to the conflicts between science and ethics and I hope we can agree that there is no conflict between science and ethics. In fact, in the international documents that give a rank ordering to the ethical rules that have to be followed, the first mentioned is always that the science, the design of the science must be adequate for its purposes. The CIOMS document states as its first requirement or in part of the discussion of that first requirement that unsound science is, and I quote, "ipso facto unethical."

And my final comment would be yes, speaking of the CIOMS document, when Susan Ellenberg presented her very interesting review of the history of data monitoring committees she omitted the point that the first mention of a requirement for a data monitoring committee in international guidelines is in the 1993 version of the

CIOMS International Ethical Guidelines. Thank you very much.

DR. LEPAY: Thank you.

Dr. Stump?

DR. STUMP: Thank you. I'll try to keep my comments brief.

First I'd like to thank the agency and Dr. Ellenberg in particular for taking the leadership role in pushing this forward. It's a long-awaited document. It's an important document. Some of us had the benefit of having small group discussions on many of these topics off and on over recent years and we know what the issues are but I think it's incredibly important that the field at large develops an awareness of these because I think it can only lead to higher quality work and getting new drugs to patients sooner.

I agree on many things but I would like to separate my thoughts into two discrete buckets. One is how we handle DMCs in later so-called pivotal trials versus how we would handle data monitoring in earlier trials. I think it's quite clear that DMCs are useful if not required for the later trials.

I have bought into the independence concept. I have realized that as a sponsor, which by the way is what I largely bring to this field, I feel that DMCs across a

variety of products, variety of therapeutic areas in biotechnology in the last coming up on 15 years; I believe that my flexibility as a sponsor is greatly enhanced by remaining blinded to data. It gives me total flexibility to manage the trial based on the changing dynamic occurring external to that trial and I really need that flexibility if I'm going to do my job.

I've had many spirited discussions and I'll say this with my biostatistics colleagues, some of whom are in the room, who have taken issue with me and my view on this and I think we heard earlier some comments about how important it is to the biostatistician's job quality to be involved in what is arguably one of the most stimulating parts of what they do. However, I have countered that that individual is incredibly valuable to me as a joint participant in clinical development planning, in clinical strategy, and I can't possibly see them as being of maximal value in that role when I know that they're unblinded to data. And I have walked that tightrope with colleagues in the past and it's not easy. I prefer if there is an equally effective alternative solution that we pursue that and maintain the full participation of my biostatistician.

I would comment we've discussed briefly that lay membership on these committees is kind of an emerging concept. I have found that to be an okay thing. I think

they bring a perspective that has been at least reported to me to be quite valuable and I've not seen problems with confidentiality being compromised in that setting. In fact, I have been involved with some programs where the program itself has had greater vitality because of the general awareness in the field that there was lay representation on the monitoring committee, so that, I do support,

The concerns I have, and I raised one of them this morning, would be whether the extension of guidance would be perceived to have to require much earlier trial monitoring. This is becoming more of a problem. Maybe some of you in the audience are as aware of that as I am.

I think there must be alternative ways to handle this. I have actually been on DMCs for phase I trials. I've constituted DMCs for phase I trials. I really haven't had a really good experience with that yet. I think there has to be a way to develop credibility for the approach we take with good medical monitoring, oversight within the sponsor of that medical monitoring function, close adherence to regulatory communications, discussions with our reviewers there as to how we're doing in that job, what data we're seeing.

The flexibility that you need at that early stage of development, those trials are seldom blinded and you

really need maximal information at that point. I would be concerned if unintended, the message in the guidance were perceived by some audiences to be you need DMCs for these very early trials. We are getting requests more and more from IRBs to field DMCs at an early stage.

We have tried to come up with a solution that I think should be helpful and that is to formally constitute an internal DRB within the sponsor. This is something that Allen Hopkins and I worked out at Genentech in our years there; it worked very well for us. It had some real advantages. It gave us a very flexible means of overseeing these early trials. It provided a group of clinical biostatistics, regulatory if need be, legal if need be, external medical consultants to join us to actually protect the project team itself from the bias of being too near the work in assessing objectively certain adverse outcomes.

It also provided a means for receiving reports to the sponsor from external committees, particularly for late trials. It was a way that we could discuss with the committee, if need be discuss with the FDA, who would see what and when and under what conditions and at what risk. I think Drs. Siegel and Temple stated eloquently the risk. Having been part of one of your case studies, Jay, it turned out okay; we did what you told us.

This internal committee is a great tool. I recommend it to any sponsor who's thinking of a vehicle for managing what is becoming a more complex infrastructure for data monitoring.

It's also an excellent tool for training internal, sponsor internal medical monitors as to interact with external committees. We try to help them learn on us, work out some of their inefficiencies due to experience before we toss them out on the field at large. We know you have a very hard job when you are actually called to be on one of our DMCs, so this has been a definite plus for us.

But overall, I think if you can pick excellent people, you write a very clear charter up front, you get everyone's buy-in--the committee, the agency--and then you move forward and I think that has worked well. If we can make sure we don't undercut our efficiency at the very early stage of drug development I think this is going to go a very long way to clarifying things for the field.

DR. LEPAY: Thank you.

I'm going to invite people to come up to the microphones for comments but I believe Dr. Califf has a comment as people are moving toward the microphones.

DR. CALIFF: I left out one important group to chastise, those of us at academic medical centers, and it

relates back to I think a common problem we have with David Stump that's really growing.

If you look at outright fraud and shedding and misrepresentation of data and the place where I think the issue of human subject protection is most difficult, it's actually in phase I trials because very often you're not talking about any therapeutic experiment. You're really talking about doing an experiment on a human being that may be quite harmful to them to learn some things that are in your interest, either as an investigator or as a company.

But how to deal with this in an efficient way when it's not big enough to have a committee with a large amount of quantitative data, I think, is very difficult. I think all of us, including the FDA, dealing with investigator INDs and the academic community really need to work on this particular issue quite a bit more.

DR. TEMPLE: Just a couple of things provoked by the comments.

I don't think there's anything in the document that suggests you can't have a multi-armed data monitoring committee to look at all the trials for a cooperative group. You might have to modify a little bit what they do. It sounds like they get very busy but there's certainly nothing in the document that suggests that's not reasonable.

I'm very sympathetic to the idea that one doesn't want to give the data monitoring committee a whole bunch of things that the IRB does and I don't think the document does. I think it says obviously they're going to be somewhat interested in the study they're supposed to be monitoring and if they just hate it, they may be in a difficult position to do it, but they're not supposed to redo what the IRB does, I don't think. And I'm skeptical about asking them to review the consent form and all that stuff. I really think that's been done already and I don't believe the document says that they need to, although if they have something to say nobody's going to tell them to go away.

Rob mentioned that sometimes company regulatory affairs groups want to know every adverse reaction, including every death, so that they can report properly to us. Just for what it's worth, that's their problem; that isn't ours. The rules make it very clear that reporting arrangements can be modified and described and made to soup the study, so if reporting every death in an outcome trial would unblind the study, they don't have to it. They just have to say who's responsible for watching it and that there's a data monitoring committee doing it. That's completely all right.

As you know, the reporting requirements can be modified considerably from what is usual and as long as everybody agrees on them, that's okay. There's a specific rule that allows that. It's not a guidance; it's a rule. So we're allowed to do that.

Dave raised the question of, if I understood you, about what you do with trials of symptomatic treatments where they've obviously shown what they set out to show and I don't think there's been a whole lot of discussion of that but I also don't think there's any need to stop the trial. I mean we replicate those trials. We do dose response studies in them. We do placebo-controlled trials in the first place, even though there's existing therapy. It's very hard for me to think that there's an obligation to stop those trials.

That said, it wouldn't be a bad idea if trials always said what the circumstances of monitoring and stopping a trial would be. It seems to me that would be important. It's a subject for another day, I imagine, but sometimes a trial that--well, as I said, we often tell people to only stop a trial early for survival. That may mean that the other combined end point might be relatively statistically extreme. The benefit to everybody is you get to look intelligently but carefully, of course, at subsets. You get to look at a longer duration of treatment, which

you're worried about; you know it doesn't reverse. There's a lot of advantages but I do think you're obliged to tell people what you're doing.

The British way of doing that is to say they don't stop a trial until it would be convincing to everybody, so they get P values out as long as your arm but I don't think there's a standard practice of actually telling people what's going on.

I just want to talk briefly about what Dr. Stump said. I think the idea that there's either an internal or internal with a little external help group watching over the way things go is a very good idea. Whether that solves the problem of a conflicted investigator in phase I is not clear to me. CBER is certainly working on that because of some difficult experiences that they've had. But it's a thorny problem and as I wanted to say before, the problem is that you have to recognize the event as an event worth noting, which means there's no substitute for the investigator. That's the only person who can recognize the event really, as a practical matter. So whether that's a matter of training or having somebody there holding hands, I don't know, but some kind of monitoring situation in that setting seems reasonable.

DR. LEPAY: Thank you.

I'd like to open this up now for discussion, if people could come to the mikes.

OPEN PUBLIC DISCUSSION

DR. FLEMING: Fleming, University of Washington.

Rob, you introduced your comments by talking about taking potshots at a number of different areas where there were concerns. I'm surprised maybe you didn't go a little bit further. Let me be specific.

We've talked a lot during this meeting in the guidance document about the important responsibility that monitoring committees have in safeguarding the interests of participants during the course of a trial. Let's suppose now the trial has reached its completion, either through an early termination of having run its course.

How are we doing in ensuring that there is timely reporting of the results from that trial to the public, both to serve the participants in the trial and external? Are we, in fact, doing fine? Is there, in fact, a responsibility ethically and scientifically that may or may not be consistently being addressed here? What is the role of the DMC in that responsibility?

DR. CALIFF: Well, I think the role could obviously be debated but I like the word you used, an independent judge. I think at least my understanding from my NIH training now in human experimentation is that the

basis of informed consent when I enroll a patient in a clinical trial is that we will be creating generalizable knowledge. If I was doing it to help that individual person then it would be unethical to do the experiment because I would be helping them by doing what I thought was right, not asking to participate in a randomized trial.

Therefore if the result is not made public I don't know how you can call it generalizable knowledge. So the question comes up if you have stopped a trial for ethical reasons do you bear a responsibility to see it through that the data's not buried? And you don't have to be a genius to see that if the trial's positive it gets out in a hurry. If the trial's negative it could be months to years to never before it ever sees the light of day.

I think this is a major problem and I don't see it diminishing. I actually see it growing right now. In our own institution we're seeing increasingly onerous confidentiality contracts, even for members of data safety monitoring committees, that would forbid you by contract from talking about the results for up to 10 years, which I think it's a violation of the basis of informed consent.

Now I could have gotten this wrong but at least that's my view of it.

You've been on a lot of committees. Now you can't get away without--do you agree or not?

DR. LEPAY: Are there any other comments from the panelists?

DR. LEVINE: I think it's certainly true that industrial sponsors commonly ask data monitoring committee members to sign these pledges of confidentiality and when the trial comes out showing a satisfactory result, usually there's considerable haste at making the information public.

I don't know exactly what the rules are about a negative result but I do want to mention very briefly two experiences. I was on one committee which recommended a stop in a trial on the basis of futility and on that occasion the corporate executives called an emergency meeting of the board of directors because they had to make an announcement to the Securities and Exchange Commission. And they had the emergency meeting at 11:30 p.m. on the day of the data monitoring committee meeting and the statement to the SEC was made right before the market opened. Then the market opened and the price of the stock dropped 33 percent in the first hour. So I was pretty impressed that that was a very rapid contribution to generalizable knowledge.

I was also on another committee where we found that a trial should be stopped on grounds of futility and although we had signed contracts, the chair of our data

monitoring committee insisted that we send a letter to the corporate offices of the sponsor saying that if they didn't do the right thing by way of reporting this event to the FDA that the members of the committee would have to consider doing that independently. We were not tested in that regard, I'm very happy to say, but that's yet another experience.

DR. TEMPLE: It does strike me for reasons that Bob just gave that bad news about products in development or about attempts to extend a product line do get out. You know, the failure of Riapro in the acute coronary syndrome was all over the papers. Everybody knew about it. A great disappointment, obviously. People would have had reasons for not wanting it be known but there it was known. And for all the reasons that you have to tell your stockholders about things, I do think they do get out. Now you must know of some things that are contrary to that.

I guess the other observation I'd want to make is that at least for academic institutions these people have organizations that set ethical standards and I don't understand why a confidentiality agreement of the kind you described is still considered ethical and I would think that there's something you could do about it.

DR. CALIFF: I have to respond to that. I want to point out one thing. I think Dr. DeMets is probably--no

offense--has probably been involved in more trials that were controversial for not reporting the results than anyone I know.

There's a big difference between a press release that says a trial was stopped and actually showing the data so that people can understand how it may relate to the patients they're currently treating or patients that they have in other trials of related compounds. There are legal reasons why companies frequently make press releases, often with long periods of latency before anything is done.

DR. TEMPLE: So it isn't the result that's hidden; it's it details.

DR. CALIFF: It's anything that would be helpful. But again this is not the majority. I think the majority are just like you said; people are responsible and they do the right thing. But some of the examples that aren't in the majority are important.

DR. STUMP: I wouldn't say that the reporting of a sponsor to be in compliance with SEC requirements is a simple task. I would say that more often than not I have been--and I've been in the situation a lot--I have been conflicted more by having my attorney say I want you to put more information into the public domain, rather than less. And I've had investigators who really wanted sanctity of that information to have it reserved for publication in

peer-reviewed journals and not have that undercut, rather than vice versa.

Maybe you've had other experiences but you've got multiple stakeholders here and this whole process can't succeed if everybody's needs aren't at least felt to be met. More often than not I'm pulled the other way, to not put lots of specific data into the press release by the investigators, rather than doing so at the request of my own lawyers.

DR. DeMETS: I think the issue is that some very large trials which have important clinical significance don't get published. Remember I said that one of the benefits is you have access to the data and one way that doesn't happen is that resources get reallocated, so that database doesn't get cleaned up ready for publication.

There's a famous case in the AIDS arena where a trial was stopped early; the database did not get cleaned up. The investigators, I think, complained, eventually published what they had. It's now in the courts or at least it was a legal situation.

There's other trials I've been involved with which are still not published. We know what they are. One's called Profile. And these things do happen.

As Rob said, it's not that the news doesn't get out. It's the details which, in fact, could be very helpful for future trials.

DR. LEPAY: We have about 10 more minutes left so I want to make sure we at least get a chance for the people who are currently standing here to address their comments or questions.

DR. SHOULSON: Ira Shoulson. I was just going to comment on this publication issue. It's very dear to my heart as an academic investigator and we insist in doing trials ourselves that not only free and unrestricted right to timely publication but those types of assurances from sponsor to do that are really hollow assurances without having the data.

So it's really access to the data and that's why we get back to data monitoring committees, that at least the point that David DeMets made is important. Having been a friend of the FDA for many decades and served there, I can just say though at this point the FDA has not been a friend in terms of supporting this issue of free and unrestricted right to publication because as far as the FDA's concerned, just so we see the data we don't care if it's published in this journal or that journal. That's okay; just so we get to analyze the data and take a look at

it, and that's certainly consistent with their mandate and the regulations that they have.

But I think at least in the context of data monitoring committees, if at least some kind of statement could be made to ensure that there is a publication, a free and unrestricted peer review-type of publication, of the data and perhaps link it to the data monitoring committee, that certainly would be of great benefit to the public in terms of generalizabilty of findings.

DR. WITTES: Janet Wittes.

I think one thing one could do that would make a big difference and would be pretty easy is to think about adding to the charters of the DSMBs something about their responsibility after the trial is over. I mean one of the things that happens is the trial is over or you have your last meeting and the trial isn't really completely over, the report isn't done, and that's the end of the responsibility. I think a little bit of addition to the charter might go a long way.

ATTENDEE: Does the data monitoring committee have any responsibility if there is a publication that results from a flagrant misanalysis of the data in which, say, a P value is reported at below 001 when a proper analysis leads to a P value of, say, .6?

DR. LEPAY: Does anyone want to take that?

DR. CALIFF: I think there is a responsibility. I think once you sign on to be a data monitoring committee member or a data monitoring person in a small phase I study that if you see something that's not--you're the watchdog. You're the independent judge and I really think that should be part of the charter.

Just quickly, I need to comment on Ira's comment about free and unrestricted. Those words are very tricky. Just on behalf of the industry side of things, about three months ago I made an offhand comment in the middle of a negotiation with industry about this right to publish. What do you think a chemistry professor's going to demand the data and come and take it from the database and try to publish it? They said it's funny you should mention that; that just happened about six months ago to our company because the university had a free and unrestricted right of any faculty member to publish the data.

So I actually don't think it should be free and unrestricted. I think it should be planned and organized and multilateral.

DR. LEPAY: Other comments among the panelists?

DR. FLEMING: If we're going to change the subject, maybe just a quick follow-up comment to my original question.

Basically my sense is that the issue of timely reporting of results after termination of a trial is not a common problem. In my own sense, in most cases people given a reasonable period of time to make sure that they understand and present a clear message, that within that period of time results are reported.

However, when you monitor a lot of trials you run into counterexamples to this. All of the problems that we have heard do, in fact, occur where results--a study hits its completion point either through early termination or running its full course and there is an extended period of time without getting results, or as they're published in the literature, as a DMC member you're very uncomfortable that this publication represents a truly objective representation of the data.

The question I don't believe we have really adequately considered is what are our responsibilities to patients to ensure that there is appropriate, timely, accurate dissemination of data once the study is completed? And there are at least two elements to this. One of those elements is what is the data monitoring committee role in this if, in fact, you become aware of something that wont' happen very commonly but on occasion does happen where you have ethical concerns and scientific concerns?

And secondly, is it proper for monitoring committees to be signing what is not standard but often confidentiality agreements that indicate that we won't release information to anyone outside of those that are involved in data monitoring committee discussions? Do we, in fact, need to ensure that such agreements aren't part of consulting contracts? Do we need to go further, as Janet says, and ensure that charters actually indicate in these uncommon settings monitoring committees, acknowledging their ethical and scientific responsibilities that could, in fact, go to the point of after the study is terminated? And, in fact, should monitoring committees then actively in these unusual circumstances carry out that ethical responsibility to ensure that if there is a problem in their perception that they are able to address that either with the FDA or the scientific community.

DR. LEPAY: Any comments?

DR. TEMPLE: That all seems desirable but the mechanism for making that so is not obvious. A data monitoring committee is arranged through a contract with a sponsor. Under what law can we or somebody else say you can't have such an agreement?

I really do think it seems an obvious thing for academic societies to at least discus and make rules about. As Rob said, free and unrestricted might be trouble but

something that says it's their job to report the truth as they see it and you won't accept agreements that bar that.

DR. STUMP: Tough question. At least my understanding of what these confidentiality agreements from a sponsor's perspective are are really an assurance that during the in-life monitoring part of the study there will be no breach of confidentiality. I don't believe they're intended to be a muzzle, if you will, for eternity.

I think that once data is in the public domain, that's substrate for any qualified scientific opinion to be expressed and I don't see why--

DR. FLEMING: In my experience there's tremendous diversity, Dave, in this and some of them are very explicit, stating that there wouldn't be any communication with the FDA, regulatory authorities or anyone outside of those involved.

DR. STUMP: I think the FDA communication is perhaps a more difficult issue, given the reporting relationship that exists. I think the way a study is meant to work and as I've heard from the agency, they really don't want DMCs reporting to them directly. They'd prefer that be through a sponsor. We certainly set up vehicles to accommodate that reporting and would certainly entertain any discussion from any DMC member--I would--of hey, I

don't like how you're handling this and we would be open in describing how we see it.

I think that the data itself certainly has to be at some point owned by the investigator. Certainly a DMC has only seen data during the in-life portion of a trial and that may or may not be representative of what the data really are at the end of the trial and I think the investigators are empowered to interpret that data, to publish it in their peer review systems in the medical literature that are supposed to oversee that so I don't know why the DMC would have to be an added portion of peer review to that process. But I hear the question; I just don't have the easy answer.

DR. TEMPLE: One of the difficulties one hears about--you guys would know better than I--is that any given investigator in a multi-center study has a lot of difficulty getting a hold of the total data. Someone has to make it available to that person. The data monitoring committee, of course, has been given the data at least at some point, even if not the final, so they're somewhat more in a position to see the whole database.

Just from our point of view, if anybody found something presented publicly as grossly distorted we'd be interested.

DR. STUMP: I think any sponsor knows that they will ultimately be standing before the agency and have to defend their policy, so we will undergo your peer review eventually.

DR. TEMPLE: But we miss things and we'd like help.

DR. STUMP: Surely not.

MR. CANNER: Joe Canner with Hogan & Hartson.

Before I change the subject I think there are some interesting situations, particularly in device trials but not uniquely, with new, unique, novel products where the company has a pretty good reason to want to suppress negative results, especially if the product is not going to be approved. There's no, at least within the United States there's no reason why a physician should have any information about a product that has not yet been approved. But that's not my area so I understand there are other issues and I'll move on to my other question.

To follow up on my question from before about unique aspects of device trials, I have a particular question about stopping criteria, something that's been mentioned throughout the day. I just need for clarification on it.

Device trials are typically not planned to be stopped early for efficacy for a variety of reasons but it

may be appropriate to stop them early for safety. But oftentimes the safety issues are not terribly obvious up front for a number of reasons, whether it be because of unexpected issues, because of the difficulty of establishing the relationship between an event and a device, lack of prior data, and also just to evaluate events in the context of a risk-benefit, where sometimes the device is being compared to something totally different, which has a totally different risk-benefit profile.

So it's very difficult up front for a sponsor to establish stopping rules but sometimes the FDA asks the company to establish stopping rules for safety in the protocol and then dictate them to the DMC and I'm just wondering if there's any clarification on that and if it wouldn't be appropriate in some instances to allow the DMC the freedom to kind of make it up as they go along and see events as they occur and to see the evidence accumulate before making any specific criteria for stopping.

DR. CALIFF: I've got to respond to your first comment because I think it's critical for people to really think about this and for at least some thought to go into a final document.

I think there are two reasons why a device that doesn't get on the market where a study has stopped early,

the results need to be known. The first is that the investigator has signed a contract with the patient to do a human experiment, the basis of which is that it's being done to create generalizable knowledge. And to not make the results public is a violation of the fundamental concept of informed consent, at least as I've been taught in my IRB training.

Secondly, there are many devices that don't get to the market that are similar to devices that are on the market and in particular circumstances where a device has failed in its testing where there's a generalizable concept, even though it may disadvantage the company that did it, it's putting patients at risk who are not in the trial, the knowledge of which would have allowed people to be treated in a more humane fashion. I think there's an ethical construct here that truly overrides the profit motive of the device company.

Obviously I feel strongly about this but I think these issues really need to be considered and people monitoring trials need to have some responsibility for making sure that the basic fundamental construct of a human experiment is adhered to.

MR. CANNER: I would agree and I'd just respond. I think you could concoct a situation though where it really would be in the best interest of both the patients

and the industry to, in the interest of trying to develop enhancements to a product, especially if it's a unique product that isn't already captured in the market, that instead of casting a pall on all further studies of that device by saying that the first go-around was negative, instead to allow the company to improve the product and come up with something that might actually work, without the bias of previous studies.

DR. CALIFF: I think there needs to be reasonable time. There are always exceptions. I agree.

DR. DeMETS: In response to your second question, I think monitoring committees themselves need to be reminded of the fact that the data are spontaneous and random and if you have no plan in place you can deceive yourself in reacting to something that is just a chance event.

Of course, in the safety business one never knows what to expect so we're always sort of making some rules up as we go, as we see new events. But to have nothing to start with, I think, is kind of dangerous. I think you need to have some plan at least to give you some navigational aids as to how to assess and remind yourself as a committee that there are these chance events. To say nothing, I think, opens the door too wide.

DR. LEPAY: We're just about at our closing time here so we'll let Jay respond.

DR. SIEGEL: On that point, the document, to the best of my recollection, does not specifically address the issue of stopping rules for safety, and correct me if I'm wrong. For efficacy they're addressed because of the need for prospective rules to ensure appropriate protection of type 1 error. That said, the word "rules" here is not used the way the FDA uses them, which is they may be stopping rules but we understand that a good DMC may, for good cause, choose to disregard those rules. Nonetheless, that should be rare and they ought to be in place and probably agreed to by the DMC, if not, as some have suggested, written by them.

I think in safety it's a different issue. It's not addressed in the document so we don't have guidance in that area. I think experience would suggest that sometimes they're used if it's the same parameters, if it's a mortality trial for mortality going the wrong direction, but experience has shown that usually there are futility rules that kick in before the safety stopping rules do, anyhow. If by the time you've reached a point where you seem to have proven harm, you earlier reached the point where the likelihood of proving success is so small that trials often get stopped for that reason.

The only other thing I would note, because it is germane to a lot of discussions we've had earlier, when safety is an issue that relates to outcomes other than the primary end point, often there's not only the issue that the safety event may be unanticipated so hard to preplan for, but it's also often critical to integrate that safety outcome in the context of the likelihood that the drug may be benefitting. And even when we've gotten unblinded data from a trial and learned unexpectedly that a drug may be or seems to be increasing the risk of a serious adverse event that wasn't anticipated, more commonly than making a decision that the trial needs to be stopped or even altered, we'll often kick that back to the monitoring committee to look at that finding in the context of the efficacy data because you might have serious bleeding in the context of a trial that's suggesting an important new benefit on mortality and it's very hard to plan in advance for how much serious bleeding should stop a trial that may be saving lives.

MR. O'NEIL: Bob O'Neil, FDA.

I was wondering if the panel had any thoughts on an issue related to the complement of where Greg Campbell started and the comment of the gentleman previously about data monitoring committee lite.

A lot of effort was put into the document to think about what data monitoring committees, which would be independent, and which trials might be eligible for that. Once you make that decision it leaves a body of trials that don't have to have this independent data monitoring committee structure, the bureaucracy of it, but the spirit of it sort of lives on, particularly if you want to do industry-sponsored trials where the industry is going to monitor the trial to some extent. There's a lot of literature and methodology these days on flexible study designs which allow you to prospectively, in the learn-confirm environment, given, as Bob indicated--Bob Temple had indicated that a lot of folks are not necessarily going through a sequence of trials. They're doing some early phase trials and they're getting into a phase III trial real fast, trying to get it all done, but most of these phase III trials are often learning trials in their own right.

So the flexible designs can drop an arm, they can drop a dose, they can up-size the trial, they can do them all in a legitimate way and this gets hard real fast. I'm concerned that this is much beyond the monitoring job that a data monitoring committee needs to do. And I guess what I'm asking is do you see that the document leaves room for how to implement in a firewall sense flexible designs where

it needs access to unblinded data and where interim decisions have to be made to get onto the next step in terms of what you do and to preserve the validity and credibility of the trial?

There's an answer to that both for the independent data monitoring committee model and there's probably another answer to that for the trial that would use a flexible design but wouldn't rise to the level of an independent data monitoring committee model. I was wondering if you had any ideas on that because this document doesn't address that right now.

DR. DeMETS: Well, I'd only comment on one specific. The document does discourage using unblinded data to adjust sample size--I think at one point it talks about that--yet we know there's research going on which says, in fact, you can do what seems to be heresy, statistical heresy. In fact, you can change the sample size based on the interim delta and do it in such a way that you don't screw up the alpha level, at least not in any way we care about.

But we're not there yet that this has been tested, examined, challenged, so these developments are probably too new, but the current document is at somewhat at odds if you take it literally, the way it's written right now. So it doesn't leave much room for some of that

and I guess this is a document that also is a living document. When we get there maybe you'll change it but right now it's kind of keeping the door pretty tight on that and things like that.

DR. LEPAY: Any other comments from the panelists?

CLOSING REMARKS

DR. LEPAY: Well, I want to thank everyone very much for their participation today. This has been very valuable for FDA. I'd like to thank our panelists of this last session.

The comments we've certainly appreciated. They will certainly be taken into account as we move forward with this document.

For those you know who may not have seen this document we encourage its circulation. Again it's open for public comment until the 19th of February. Please participate in our process here. We thank you very much again for your attendance.

[Whereupon, at 5:05 p.m., the meeting was adjourned.]

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